THE PNEUMATIC TOURNIQUET : A LITERATURE REVIEW AND STUDIES TO IMPROVE ITS SAFETY IN CLINICAL PRACTICE

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by

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Signed

Gordon Irving

August 1983

DECLARATION

I, G. Irving, declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

I empower the University to reproduce for the purpose of research either the whole or any portion of the content in any manner whatsoever.

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ABSTRACT

Pneumatic tourniquets are commonly used to produce bloodless operating fields in lower limb and hand surgery. Until recently, relatively little attention has been paid to the possibility that the tourniquet may cause neuromuscular damage. Although a low incidence of permanent neuromuscular damage has been reported, recent studies suggest that partial muscle denervation, lasting for several months, may be present in 71% of patients undergoing surgery involving the use of a tourniquet (Dobner and Nitz 1982).

This thesis, includes two studies designed to investigate different problems in the use of the pneumatic tourniquet. The first investigated the use of local hypothermia to protect the ischaemic muscle during a prolonged tourniquet application; the second studied the accuracy of the automatic tourniquet pressure apparatuses in regular clinical use in Western Cape hospitals.

(i) Studies of the effect of local hypothermia on tourniquet-induced muscle ischaemia

Although local hypothermia has been advocated as a method to increase tourniquet time safely from two to four hours (Seki 1980), little experimental data has yet been collected to prove the efficacy or otherwise of this procedure. Thus an animal model was devised in which the effect of hypothermia on skeletal muscle made ischaemic by the use of the tourniquet was compared to ischaemic muscle that was kept at room

temperature. Under general anaesthesia, the upper limbs of 21 Landrace pigs were subjected to a tourniquet application of three hours at 500 mmHg pressure, the opposite limb acting as a control. In ten pigs (hypothermic group), the tourniquet (ischaemic) limb was cooled by surrounding it with cold packs; the ischaemic limbs of the remaining 11 pigs (control group) were exposed to room temperature. Measurements made included : serum lactate, sodium, potassium and calcium levels, serum pH, creatine kinase activity and nasal, skin and muscle temperatures before, during and after tourniquet application. Muscle biopsies were taken from muscle below the site of the tourniquet before the application and at ten minutes after release of the tourniquet. The muscle biopsies were stored in liquid nitrogen for subsequent analysis for glycogen content and phosphofructokinase activity. The pigs were monitored for six days after surgery before being re-anaesthetised for a second tourniquet application to the same limb at 500 mmHg pressure for two hours, but without the application of hypothermia. Muscle biopsies were again taken prior to and ten minutes after tourniquet release. Four days later, the pigs were sacrificed with an overdose of penthothal. Muscle biopsies were taken from both the limb which had had the two tourniquets applied and the control limb.

These experiments established the following :

1. When compared to the normothermic ischaemic limb, the hypothermic ischaemic limb had higher pH, lower venous lactate levels and a slower rate of muscle glycogen utilisation. These findings

indicate that hypothermia reduced oxygen-independent glycolysis during tourniquet application.

2. On tourniquet release, potassium levels in the venous effluent blood draining the hypothermic, ischaemic limb were lower than those measured in the blood draining the control, ischaemic limb. This indicates that the hypothermia reduces the extent of tourniquet-induced muscle cell damage.
3. The muscle and skin temperatures of the ischaemic hypothermic limb returned rapidly to control values on tourniquet release, whereas these temperatures in the normothermic ischaemic limb remained significantly elevated. This indicates that hypothermia prevented the development of a marked tourniquet-induced inflammatory response
4. Muscle glycogen and phosphofructokinase activities were significantly higher ten days after the initial tourniquet in the hypothermic, ischaemic limbs, whereas these values were reduced in the normothermic, ischaemic limb. This indicates that hypothermia preserved the viability of muscle subjected to two prolonged ischaemic insults.

These findings provide strong evidence that (i) the prolonged application of a tourniquet produces significant muscle damage and (ii) that locally-applied hypothermia decreases the magnitude of this damage. The nature of this protective effect is uncertain but may relate to the slowing of metabolic rate during ischaemia and a reduced inflammatory response during recovery.

(ii) Study of pneumatic tourniquet apparatus in clinical use.

Thirteen tourniquet apparatuses in clinical use in Western Cape hospitals were studied. A protocol was drawn up which measured the accuracy, stability and the pressure compensation mechanism of the apparatuses. A thorough visual examination for any external damage was also carried out at the same time. Only two of the machines were found to work satisfactorily. Of the remaining eleven, eight had inaccurate gauges when measured against an accurately calibrated pressure manometer, and the remainder showed defective pressure compensation mechanisms.

This study demonstrated a need for such a standard protocol to check all tourniquet apparatuses in clinical use. Recommendations from this study have been made to the various hospitals and it is hoped that this will help decrease the risk of the tourniquet procedure by removing defective equipment from regular use.

(iii) Further Studies

The study concludes by considering further research areas into the effects of tourniquet application. Clinical trials based on some of these findings are currently underway.

ABBREVIATIONS

ADP	Adenosine 5'diphosphate
AMP	Adenosine 5'monophosphate
ATP	Adenosine 5'triphosphate
β	Beta
CK	Creatine kinase
^{51}Cr	Radio-active chromium
EDTA	Ethylene diaminetetra acetate
F6P	Fructose 6-Phosphate
G6P	Glucose 6-Phosphate
G1P	Glucose 1-Phosphate
G6PDH	Glucose 6-Phosphate dehydrogenase
H+	Hydrogen ion
K+	Potassium ion
KCN	Potassium Cyanide
KOH	Potassium Hydroxide
L	Litre
LDH	Lactate Dehydrogenase
M	Molar
mg	milligrams
MDH	Malate Dehydrogenase
$MgCl_2$	Magnesium Chloride
ml	Millilitre
mM	millimolar
mmHg	millimetres of mercury

Na^+	Sodium ion
^{22}Na	Radio-active sodium
NAD+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide (reduced) form
NADP	Nicotinamide adenine dinucleotide phosphate
NaOH	Sodium Hydroxide
nm	nano metres
O_2	Oxygen
PCA	Perchloric acid
PO_2	Partial pressure of oxygen
rpm	revolutions per minute
SNF	Supernatant Fluid
Tris buffer	Tris-(hydroxymethyl)-aminomethane
U	units
μ	micron
^{133}Xe	Radio-active Xenon

CHAPTER ONE

INTRODUCTION AND SCOPE OF THE STUDY

"Anoxia not only stops the machine, it wrecks the whole machinery".

Haldane 1926

As an anaesthetist, I have often watched the pneumatic tourniquet or Esmarch constrictive bandage being wrapped around a patient's limb. It seemed to me that the force with which the bandage was applied, or the pressure at which the pneumatic cuff was set, were chosen somewhat arbitrarily. Similarly, I noted that various surgeons had different opinions about the "safe" duration of tourniquet application. In my experience, these opinions ranged from thirty minutes to four hours. However, I could find no literature describing in full detail the hazards of what has become an extremely common surgical procedure. Thus I began to compile a comprehensive review of the literature on the effects of tourniquet application on neuromuscular and vascular function.

Whilst the pneumatic tourniquet is an invaluable aid to the surgeon, lessening the muscular damage caused by the tourniquet is of great importance to the sportsman undergoing surgery, to expedite his or her rehabilitation and early return to sport. Thus, it became apparent to me that a method for increasing the safety of the tourniquet application was required. It seemed logical that, as a start, one should look at the protective effect local cooling of a limb with chemical ice packs would have on a muscle undergoing a prolonged tourniquet application. Chemical ice packs used in the study reported, have the advantage that they do not create a mess in the operating theatre, they are easily applied to the ischaemic limb, and they allow easy access to the operation site. Use of the commercially available ice packs in this way has, to my knowledge, not been reported previously. Thus, the following

studies were undertaken, based on my dual interests :

(i) as an anaesthetist frustrated by the lack of a comprehensive review and recommendations on the effects of the pneumatic tourniquet, and

(ii) as a sportsman worried about the effect on the athlete's rehabilitation after operations involving the use of the tourniquet.

The following thesis is the result of those studies.

CHAPTER TWO

A REVIEW OF THE LITERATURE ON THE EFFECTS OF TOURNIQUET APPLICATION ON VARIOUS MORPHOLOGICAL, BIOCHEMICAL AND PHYSIOLOGICAL PARAMETERS.

"The use of the tourniquet is a safe but certainly not innocuous procedure".

Bruner (1970)

2.1 HISTORICAL BACKGROUND

Constriction devices to control haemorrhage have been used since at least Roman times. The name "tourniquet" was first used by Jean Louis Petit in 1718 to describe his compression screw for haemostasis (tourner = French "to turn") and various modifications of Petit's apparatus remained in use until the end of the 19th Century. Lister, in about 1864, was the first surgeon to describe the use of the tourniquet for surgery, other than amputation, when he operated on a tuberculous wrist joint. He expressed pleasure at the bloodless operating conditions the tourniquet created. Lister also emphasised the importance of elevating the limb prior to tourniquet application to drain the venous blood from the limb (quoted by Klenerman 1962).

In 1873 the use of the flat rubber bandage tourniquet was introduced by Professor Johann Friedrich August von Esmarch, Professor of Surgery at Kiel. He also described the use of his bandage as a means of expressing venous blood from the limb, an application still in use today (Esmarch 1873).

In 1904 Harvey Cushing introduced the pneumatic tourniquet, abandoning the rubber tourniquet of Esmarch because of the danger of nerve palsy and the difficulty in its re-application during an operation. With minor modifications, the Esmarch bandage and the gas pressurized pneumatic cuff remain the main methods for creating and maintaining a bloodless field for limb surgery, the limb first being exsanguinated by either elevation or the use of the Esmarch bandage.

2.2 PRESENT DAY USE OF THE TOURNIQUET

In modern practice, the tourniquet is used for various procedures :

(1) Tumours of the limbs. There is evidence that dissemination of tumour emboli is reduced when biopsy or amputation for malignancy is carried out in a 'bloodless field' (Peltier, 1956).

(2) Regional chemotherapeutic perfusion of limbs (Creech et al., 1958).

(3) To control the flow of blood during operations on the scalp (Orticochea, 1977).

(4) The creation of a bloodless field for limb surgery. This is the most common modern application for the tourniquet.

At present, in North America, an estimated 10,000 pneumatic cuffs are used annually in more than one million surgical procedures (Kidde Company, 1979 - quoted by McEwan and McGraw 1982). Although no figures are available for South Africa, it is reasonable to assume that, on a per capita basis, similar numbers are involved.

It is also apparent that complications do occur due to the pneumatic tourniquet and may be more frequent than previously suspected. Dobner and Nitz (1982) reported that 71% of 24 patients undergoing menisectomies under tourniquet ischaemia, had abnormal electromyographic find-

ings six weeks after operation. Similar results were found by Weingarden et al. (1979). Muscle strength, measured by maximum isometric tension development, contraction and half relaxation times, of the muscles lying under and distal to a tourniquet, was reported by Patterson and co-workers (1981). Six days after a three hour tourniquet, compressed muscle tension was reduced to approximately 80% of the control value whilst, in the distal muscle, tension development varied from normal to 64% of the control value. They concluded that muscle strength recovery may take more than a week to recover after a three hour tourniquet application. Thus, several authors have advised that the tourniquet be avoided where possible, especially if the person involved is a trained athlete who wishes to make an early return to his or her sport (Dobner and Nitz 1982, Eriksson 1981). Ward (1976), reporting the avoidance of tourniquet use by the elevation of the hand being operated upon, noted a marked decrease in post-operative swelling and earlier return to function.

However, many surgeons still believe that the procedure of tourniquet application is extremely safe and reliable. They contend that the procedure causes very few clinical complications whilst affording a clear surgical field at operation. Thus, it seems likely that the pneumatic tourniquet will continue to be used for even minor procedures in the foreseeable future. This being the case, it becomes essential to understand the potential complications of this procedure and to develop techniques that can reduce or even eliminate these risks.

2.3 MORPHOLOGICAL DAMAGE TO MUSCLES

Harman (1947) was one of the first to describe marked changes in skeletal muscle fibres after tourniquet application for between two to four hours on rabbit hind limbs. He showed that the longitudinal striations present in the fibres disappeared after two to four hours' ischaemia and cross striations became conspicuous. Longer ischaemic periods of up to 18 hours were associated with the appearance of anisotropic Bowmans discs, which he considered to be "true degenerative forms and not artefacts caused by fixation and sectioning".

Solonen and Hjelt (1968), in human striated muscle and Heppenstall et al. (1979) in the quadriceps muscles of dogs, noted granular degeneration in the muscle cells after 30 minutes of tourniquet ischaemia. These changes were even more marked after one hour of tourniquet application. Capillary damage was also noted after thirty minutes, but minutes, but remained mild until about two hours' ischaemia when hyalinisation and an increase in the inflammatory cell reaction was noted. Interstitial oedema was present after one hours' tourniquet application and, after two hours, was more marked and associated with haemorrhage. Twenty-four hours after tourniquet release the oedema had progressed further (Harman, 1947, Heppenstall et al. 1979).

J'ozsa and co-workers (1980) performed serial biopsies on the intrinsic hand muscles of patients undergoing reconstructive surgery under tourniquet ischaemia. They found only limited ultrastructural alterations after an ischaemia time of up to 120 minutes. Except for a reduction in

the number of glycogen granules in both red and white fibres, they found no immediate effect of ischaemia on any other component of the fibres. Mitochondrial, myofilamental and nuclear alterations were NOT found. However, there was extracellular oedema which increased in severity with the duration of tourniquet application. Swelling of the endothelial cells was present after 30 minutes and was associated with obliteration of the capillary lumen, although extravasation or disruption of the capillary wall was not observed.

In rhesus monkeys, Patterson and Klenerman (1979) reported that more damage occurred to those tissues directly under the tourniquet than at distal sites. In contrast to the findings of J'ozsa et al. (1980), they noted that the mitochondria appear to be very sensitive to ischaemia, and showed changes within one hour of tourniquet application. Mitochondrial structure returned to normal only three days after a three hour tourniquet application and seven days after a five hour application. Similar results were found by Tountas and Bergman (1977).

It has been reported that white Type II (fast twitch) muscle fibres may be more protected from an ischaemic insult than are red, Type I (slow twitch) fibres, possibly because they contain fewer mitochondria (Jennische et al. 1979). However, Heppenstall et al. (1979) and J'ozsa et al. (1980) were unable to find any difference between the tolerance of slow and fast twitch muscle fibres to ischaemia.

SUMMARY OF MORPHOLOGICAL DAMAGE TO MUSCLES

The reports differ with respect to the time of onset and extent of the damage caused by tourniquet ischaemia. This may be due to differences in the various muscles biopsied, the different animal species used and the different sites at which the muscles were biopsied, whether distal to, or directly beneath the tourniquet. Consistent findings were oedema and associated capillary endothelial damage starting within half an hour of tourniquet application. This oedema increased in severity with the duration of the application and continued for at least 24 hours after tourniquet release. Whether the different muscle fibres have different sensitivities to ischaemia awaits further study.

2.4 NEUROLOGICAL DAMAGE

A. Clinical Studies

The incidence of clinically apparent nerve damage is difficult to determine as adequate prospective studies utilising large numbers of subjects have not yet been published. Early reports (Lejars (1912), Eckhoff (1932), Bruner (1951) have warned of adverse effects to nerve function and Moldaver (1954) reported seven cases of tourniquet paralysis which he believed to be largely mechanical and not ischaemic in origin.

A retrospective questionnaire survey by Middleton and Varian (1974) in Australia, provided an 'educated guess' that the average incidence of tourniquet-induced peripheral nerve damage was 1 in 8,000 operations. The figure was higher for the arm (1 in 5,000) than in

the leg (1 in 13,000). Sixty percent of the reported upper limb and all the lower limb palsies were caused by the use of the Esmarch bandage, and all except one tourniquet had been applied for less than 90 minutes. Only two paralyses failed to resolve completely; of the others, the majority recovered in four to five months, although some required up to 12 months for full clinical recovery. Although the validity of this survey and the assumptions made are open to criticism, it emphasises that tourniquet application, especially with the Esmarch bandage, can cause serious damage to peripheral nerves.

Rorabeck and Kennedy (1980) suggested that many tourniquet palsies were, in fact, not reported because of medicolegal implications; thus the true prevalence may be under-estimated. Indeed, successful litigation for a tourniquet-induced paresis has been filed in the United States (Wachsman 1978). Rorabeck and Kennedy also presented case reports of five patients with sciatic nerve palsy. In one, the palsy had not completely recovered even six months after the tourniquet application.

Incorrect pressure gauge readings have been associated with many nerve palsies (Prevosnik 1970, Fry 1972, Medical Devices Alert 1978, Bruner and Calderwood and Dickie 1972, Flatt 1972, Hamilton and Sokoll 1967). Rudge (1974) reported a case of total median, radial and ulnar nerve paralysis in a patient who had undergone tourniquet application for a total of 60 minutes, 40 minutes plus

20 minutes, separated by a four minute interval. The aneroid gauge of the pneumatic tourniquet used in this operation was stated to be accurate. After four-and-a-half months, only 50% of the median and ulnar nerve function had returned.

Thus, complete 'tourniquet paralysis' is a well recognized complication of the procedure, but the incidence appears to be small and many surgeons may never see one such case in a lifetime (Funk, 1980). It is reported that even though the motor deficit may be severe, there may be only minimal sensory loss (Trojaborg, 1977). The identification of minor degrees of muscle weakness in the face of normal sensation is difficult. However, recent electromyographic (EMG) studies are beginning to show the extent of the 'hidden' neuromuscular damage caused by the tourniquet.

Saunders et al. (1979), reporting on a larger trial initiated and first-reported by Weingarden et al. 1979, evaluated limb EMG changes after tourniquet application. Forty-nine patients were evaluated six weeks after routine menisectomies, all of which were performed under tourniquet. Eighty-five percent of the patients with a tourniquet time of more than 60 minutes had EMG signs of motor denervation distal to the site of the cuff, usually involving muscles served by the femoral and posterior tibial nerves. Twenty-two percent who had had a tourniquet time of less than 15 minutes also had abnormal EMG's (Table 1). An abnormal EMG was defined as the presence of positive sharp waves, with or without fibrillation

potentials, a decrease in the number of voluntary motor unit action potentials and an increase in the polyphasic nature of the motor unit action potentials. The abnormal EMG's took two to five months to resolve - the shorter the tourniquet time, the faster the recovery.

Table 1

EMG Abnormalities six weeks' post-tourniquet (Saunders et al. 1979)

No. Patients	Tourniquet Time	Abnormal EMG's	
		Number	%
13	60 minutes	11	85
14	30 - 60 minutes	10	71
12	15 - 30 minutes	7	58
9	15 minutes	2	22

A similar study by Dobner and Nitz (1982) reported EMG abnormalities in 17 (71%) of 24 patients six weeks after menisectomy under tourniquet. No statistical correlation was found between the duration of the tourniquet and the prevalence of abnormal EMG's showing partial denervation. As in the study of Saunders et al. (1979), the muscles supplied by the femoral and posterior tibial nerves were involved predominantly. One subject showed EMG abnor malities six weeks after a tourniquet application of eight minutes at a pressure of 340 mmHg. In a control group of 24 subjects who had had similar operations, but without a tourniquet, no evidence

of EMG abnormalities at six weeks or later was found. The two groups' functional capacity were measured by recording the height obtained with a one-legged jump test and by the maximum resistance generated by the quadriceps femoris muscle group during progressive resistive exercise. Those subjects with no EMG abnormalities (i.e. 7 out of 24 of the tourniquet group and all 24 of the non-tourniquet group), had functional capacities 71% and 79% respectively when compared with the non-operated leg. Those subjects who had EMG signs of denervation (71% of the tourniquet group and none in the no-tourniquet group) had functional capacities of only 39% when compared to the normal leg. The differences in functional capacities persisted until the EMG abnormalities resolved, which took between three and six months.

Femoral nerve conduction studies were carried out in 31 patients at six weeks post-tourniquet but were discontinued when no abnormalities were found. The authors suggested that the six week period between the operation and the testing may have allowed any subtle conduction defects in the femoral nerve sufficient time to recover.

B. Proposed Mechanisms and Sites of Neurological Damage

Two main mechanisms are postulated as the cause of nerve damage following tourniquet application; the first is ischaemia, and the second is the pressure and shearing effect of the tourniquet.

The Ischaemic Insult

Substrate depletion and the accumulation of the metabolites of hypoxia in ischaemic tissue can disrupt the normal electrolyte transfer both of the nerve itself and of the more sensitive motor unit (Lundborg, 1970). Confirmation of the role ischaemia may play was provided by Matsen and co-workers (1976) who used an airsplint inflated to 80 mmHg in awake volunteers. When the limb was elevated, ischaemia was increased and there was a greater slowing of nerve conduction and a greater decrease in evoked muscle action potentials.

Some workers believe that the fastest conducting nerve fibres are more sensitive to ischaemia (Lundborg, 1970 and 1972, Fox and Kenmore, 1967); others (Nielsen and Kardel, 1974) that the slower nerve fibres are more sensitive, and yet others (Ruskin et al. 1967) that ischaemia produces an equal decrease in conduction velocity in all nerve fibre types. On the other hand, Tamada and co-workers (1981) have shown that the largest myelinated fibres are the first to be affected. Using awake human volunteers, they showed that somatosensory evoked potentials (SEP) from Erbs point, which is served primarily by large myelinated fibres, were the first to fail. They also state that selective abnormalities of SEP could occur in disorders of the peripheral nerves, perhaps indicating different sensitivities of the different myelinated fibres to various insults.

The general consensus is that the initial effect of an inflated cuff on nerve conduction is probably due to ischaemia and is rapidly reversed if the tourniquet application is brief (Lundborg 1970, Yamada et al. 1981, Matsen et al. 1976). This does not, however, explain the persistant EMG abnormalities found in both Saunders et al. (1979) and Dobner and Nitz's (1982) studies in patients who had tourniquet times of less than 15 minutes.

Direct Mechanical Pressure

The second postulated cause of nerve damage is that it is due to the direct pressure, plus the shearing stresses created in the tissues by the tourniquet.

Ochoa et al. (1972) investigated the damage caused by a tourniquet inflated to 1000 mmHg for 1 - 3 hours around the knees of baboons. Single teased fibres were studied in transverse sections under the electron microscope for up to six months after the tourniquet application.

Their findings were :

(a) In the first few hours after tourniquet release, nerve damage was restricted to areas underlying the edges of the cuff, suggesting that this was a result of direct pressure trauma. The early changes consisted of dislocation of the Nodes of Ranvier of the large myelinated fibres. Invagination of these Nodes was accompanied by the infolding of the myelin with movement of the nodal axoplasm and axonal membrane away from the point of junction of the

two Schwann cells. Other changes, such as partial or complete rupture of the myelin lamellae in the invaginated area, were also seen.

(b) By the end of the first week, demyelination had followed the invagination, always in the direction away from the cuff towards uncompressed tissues, both distally and proximally.

(c) The demyelination lesions which persisted for weeks and even months recovered by gradual remyelination. The authors were unsure whether this remyelination was due to lateral extension of myelin from an intact region, as proposed by Allt (1969), or whether the thin tapered myelin was due to the persistence of partial demyelination.

(d) On recovery, the nerve showed a mixture of normal, demyelinated and thinly remyelinated fibres in the areas underlying the tourniquet cuff edges. No demyelination lesions occurred directly under the body of the cuff.

These workers also studied nerves distal to the cuff but could find no evidence of demyelination after 2 - 3 hours' ischaemia with the cuff at 1000 mmHg pressure.

Others have found that the application of high tourniquet pressures (1000 mmHg) causes a conduction block in the nerves underlying the

tourniquet (Fowler et al. 1972, Gilliatt et al. 1974, Rorabeck 1980). Gilliatt et al. (1974) and Rorabeck (1980) both reported that conduction blocks appear to develop at the site of the nerve which had been directly under the proximal edge of the tourniquet cuffs. Gilliatt et al. (1974) also reported that conduction blocks occurred under the distal edge of the tourniquet cuff in two of the four monkeys they studied.

Rorabeck (1980) reported that the duration of recovery in the sciatic nerve of dogs was directly proportional to the duration of the tourniquet application and the pressure to which the cuff was inflated. Similar results were found by Hurst et al. (1981) who examined conduction velocities of the median and ulnar nerves of humans after a tourniquet of 300 mmHg pressure. These authors found that the conduction velocity had returned to only 75% of pre-tourniquet levels even when measured two hours after release of the tourniquet. The delay was again localised to the area of the nerve which had been under the tourniquet.

Ochoa and co-workers (1972) point out that the pressure gradient in the tissues would be greatest between the parts directly under the edge of the cuff and those on either side. Also, with a relatively wide cuff, the gradient would be maximal under the edges of the cuff and least at its centre. Rorabeck (1980) also suggests that this shearing force would be greatest at the proximal edge of the cuff due to the conical nature of the limbs of most of the experimental animals. The nerve itself appears to be very resistant to directly applied pressure as demonstrated by Grundfest (1936), who showed that pressures of over 1000

pounds per square inch were necessary to cause a conduction block in isolated frog nerves.

Summary of Neurological Damage

That complete nerve paralysis can follow tourniquet application is well reported, although the incidence would appear to be low. The paucity of reports may possibly be due to medico-legal considerations. On the other hand, the incidence of previously undetected partial muscle denervation following a tourniquet application is reported to be extremely high, up to 71% in one series. This, coupled with the fact that the return to normal nerve and muscle function may take up to six months, indicates that nerve damage caused by the tourniquet is a greater problem than previously suspected.

Ischaemia and direct pressure to nerves seem to cause little lasting damage. However, the large shearing forces between the tissue under the edge of the tourniquet cuff and the non-pressurised tissue, which are exaggerated by the conical nature of the limb, appear to cause a demyelinating lesion in at least some of the nerve fibres underlying the tourniquet edge. Whether the demyelination lesions caused by cuff pressures of 1000 mmHg occur in clinical practice, where lower cuff pressures (500 mmHg) are used, remains to be established.

2.5 METABOLIC AND BIOCHEMICAL CHANGES IN BLOOD AND SKELETAL MUSCLE OF THE ISCHAEMIC LIMB.

A. Serum Creatine Kinase (CK) Activity

Creatine kinase is found mainly in striated muscle (Tanzer et al. 1959, Pausescu et al. 1976) and its measurement in blood is used as an indicator of muscle injury.

Chiu et al. (1976) measured CK levels in dogs who had undergone pneumatic tourniquet applications to their hind limb for periods of one, two or three hours. Control dogs showed only a slight rise in CK activity during anaesthesia. After the release of a one hour tourniquet, there was no significant difference in serum CK levels between controls and the dogs who had had tourniquets applied. After the release of a two hour tourniquet occlusion, there was a delay of up to an hour before the regional venous CK activity began to rise. It was suggested that this was due to the no-reflow phenomenon as first proposed by Strock and Majno (1969). After a three hour tourniquet application, the CK activity in the first venous blood sample drawn 15 minutes after release had risen significantly. These authors and others (Heppenstall et al. 1979), found that by releasing the tourniquet for 15 minutes every hour for three hours, the CK and pH responded as if the tourniquet had been applied for only one hour. They concluded that interrupting the ischaemia time by 15 minutes in every hour, could safely prolong the tourniquet time, and this would avoid excessive muscular damage. It should be noted that these workers monitored the CK

activity for only two hours after tourniquet release, whereas the CK activity continues to rise for 24 - 48 hours after tourniquet removal (Santavirta et al. 1978a).

Chiu et al. (1976) postulate that CK is only released after a total period of three hours' ischaemia (i.e. either three hours' total tourniquet time, or two hours' tourniquet time plus one hour of no-reflow after tourniquet release), and considered that one hour of total ischaemia caused minimal cellular derangement to the skeletal muscle of dogs.

Modig et al. (1978) found no difference between the initial rise of CK in 15 patients who had had a tourniquet applied for approximately two hours and 76 controls undergoing anaesthesia without tourniquet. However, when the last blood samples were taken some 2½ hours later, the CK levels were still rising and were higher in patients who had had tourniquets applied.

Thus various authors have used serum CK activity as an index of muscle cell damage after tourniquet application. There appears to be a delayed rise in serum CK activity after two hours' ischaemia. After three hours' ischaemia, CK activity in the effluent blood rises rapidly after tourniquet release.

B. Skeletal Muscle High Energy Phosphate Content

Several authors have reported only moderate or no lowering of adenosine triphosphate (ATP) tissue levels after up to two hours'

tourniquet application (Haljamäë and Enger 1975, Larsson and Hultman 1979, Stock and Isselhard 1972, Haggmark et al. 1981). Phosphocreatine levels, however, begin to fall after four minutes and reach 32% of control levels 20 minutes after the start of ischaemia (Harris et al. 1975). The fall in phosphocreatine levels is progressive, reaching 60% of the baseline levels, 60-90 minutes after the onset of ischaemia, and being almost completely depleted after two hours' ischaemia (Larsson and Hultman 1979, Haljamäë and Enger 1975). The rate of phosphagen depletion appears to decrease with increasing tourniquet time, possibly due to a fall in temperature of the ischaemic limb (Haljamäë and Enger 1975). After tourniquet release, the return to baseline phosphocreatine levels is rapid; within five minutes after an ischaemic time of up to two hours (Haljamäë and Enger 1975, Larsson and Hultman 1979).

A tourniquet time of three hours and more caused falls in adenosine triphosphate, as well as in phosphocreatine levels. Stock et al. (1971) showed almost complete breakdown of phosphagens after three hours' tourniquet in rats. The levels were still somewhat lower than the baseline even after a one hour recovery period. After four hours' tourniquet ischaemia, normalisation of tissue phosphagen levels required several weeks and, even after three weeks, phosphocreatine levels were only 76% and adenosine triphosphate levels only 37% of pre-tourniquet levels. In these experiments, the decrease in temperature of the ischaemic limb was prevented by maintaining the environmental temperature at 28°C.

Stock and Isselhard (1972) caused renal failure and tourniquet shock on release of a five hour tourniquet application. There was almost complete phosphocreatine depletion after two to three hours' ischaemia and, at the end of the five hours, the ATP level was only 30% of the control. On release of the tourniquet, phosphocreatine but not adenosine triphosphate showed significant recovery.

Jennische et al. (1979) subjected cat hind limbs to two hours' tourniquet ischaemia and found different degrees of phosphagen depletion in red, slow twitch (Type I) and white, fast twitch (Type II) fibres. Type II fibres showed no significant decrease in ATP or phosphocreatine levels after two hours' ischaemia, but a 40% decrease was seen in phosphagen levels in Type I fibres. This may be due to the red Type I fibres' dependency on aerobic metabolism, whereas the Type II fibres are better adapted for oxygen-independent glycolysis.

Miller and co-workers (1979) have suggested that the anatomical location of the muscle with respect to the site of tourniquet application, is important in assessing the effect of tourniquet ischaemia. In monkeys, 24 hours after a 2½ hour tourniquet, they found a significant fall in phosphocreatine levels in the vastus lateralis muscle, but not in the anterior tibial muscle. They postulated that this probably reflected a direct crush injury by the tourniquet to the vastus lateralis muscle.

Thus, it seems that the muscle phosphocreatine content is rapidly depleted during tourniquet ischaemia. Adenosine triphosphate levels are, however, well preserved until after two hours' tourniquet application. Thereafter these levels also begin to decline. The rate of recovery to pre-tourniquet phosphocreatine and adenosine triphosphate levels is proportional to the duration of tourniquet application. Several weeks are required before normalisation of phosphagen stores after a four hour tourniquet application. Other factors, such as differing muscle fibre types and the type of trauma, whether ischaemic or ischaemic plus pressure, also appear to be important.

C. Skeletal Muscle Glycogen Content

Marked decreases in muscle glycogen, proportional to the duration of tourniquet ischaemia have been shown (Larsson and Hultman 1979, Stock et al. 1971). The rate of recovery of glycogen stores to pre-tourniquet levels is also proportional to the tourniquet duration. After a 4 hour tourniquet, muscle glycogen levels took 6 weeks to return to normal and, after a 5 hour tourniquet application on dogs, there was little sign of any recovery (Stock et al. 1971).

D. Blood Glucose Levels

Glucose levels of the blood in the ischaemic limb consistently fell to 23% of pre-ischaemic levels after 30 minutes of tourniquet ischaemia in monkeys (Děry et al. 1965).

E. Lactate Levels

Muscle Lactate Levels

Significant increases in muscle lactate levels, within 60 - 90 minutes of tourniquet induced ischaemia, have been reported (Haljamäë et al. 1975, Haggmark et al. 1981, Jennische et al. 1979). Experimental and clinical findings by Larsson and Hultman (1979) showed a 10 - 20 times rise in muscle lactate production between the second and third hour of tourniquet ischaemia. This corresponds closely to the lowest values of muscle glycogen found in rat and dog experiments (Stock et al. 1971, Stock and Isselhard 1972).

On release of a 90 - 150 minute tourniquet application, muscle lactate levels fall gradually (Larsson and Hultman 1979). The levels are still raised 5 minutes after tourniquet release but are normal when measured 30 minutes later. Haljamäë and Enger (1975) reported a complete return to normal muscle lactate levels, five minutes after tourniquet ischaemia of up to 60 - 90 minutes in humans. However, in dogs, approximately one hour was needed for tissue lactate normalisation after a 3 hour period of experimental tourniquet ischaemia (Haljamäë and Enger 1975).

Blood Lactate Levels

In monkeys, Déry and co-workers (1965) found no change in venous lactate levels for the first 30 minutes after tourniquet release. Thereafter, lactate levels rose steadily. Others have found high

lactate levels in the first venous sample drawn from the limb after removal of the tourniquet (Heppenstall et al. 1979, Haljamäë and Enger 1975, Dahlbäck 1970).

The correlation between the duration of ischaemia and the time needed for the lactate to return to pre-tourniquet levels after tourniquet release, has been suggested as evidence of both the existence and the severity of a partial no-reflow phenomenon (Dahlbäck et al. 1970, Harman 1948, Strock and Majno 1969).

Heppenstall et al. (1979) reported that releasing the tourniquet for ten minutes every hour prevented the immediate elevation of blood lactate after a 3 hour tourniquet application. This suggests that regular hourly release of the tourniquet prevents an accumulation of the products of oxygen-independent glycolysis. The blood lactate/pyruvate ratio in the muscle of the ischaemic limb is significantly increased during the tourniquet application and for the first few hours after tourniquet release (Déry et al. 1965, Enger et al. 1978), confirming oxygen-independent glycolysis which continues after tourniquet release.

After 4 or more hours of ischaemia, muscle cells are morphologically changed and areas of anoxic tissue remain, thus prolonging the return to resting lactate levels (Chiu et al. 1976, Rhamer et al. 1977, Stock and Isselhard 1972, Tountas and Bergman 1977). Thus, the longer period needed for tissue, as compared to blood

lactate normalization, may be due to the combined effects of a slow washout from the tissue and continuing lactate production in hypoxic areas.

Thus tourniquet ischaemia activates oxygen-independent glycolysis producing elevated lactate levels in muscle and in venous blood draining the ischaemic limb. The rate of lactate production appears to be greatest between the second and third hours' of continuous tourniquet application. Intermittent interruption of the tourniquet for 10 minutes in every hour appears to prevent a significant lactate build-up. It has been proposed that the slow equilibration between tissue and blood lactate levels after tourniquet release indicates the no-reflow phenomenon. Persistently elevated lactate levels after tourniquet release may indicate severe alterations in muscle cell metabolism.

F. Blood Acid-Base Levels

Hydrogen Ion Concentration

During the tourniquet application, features of gross metabolic acidosis occur, the pH of the blood in the ischaemic limb falls from 7,38 to pH 7,1 after 30 minutes and to pH 6,6 after two hours (Déry et al. 1965). Similar results were reported by Shaw-Wiglis (1971).

The time for normalisation of venous pH after a one hour tourniquet has been reported to be 10 - 15 minutes in humans (Shaw-Wiglis

1971), 25 - 30 minutes in dogs (Chiu et al. 1976), and 20 minutes in rhesus monkeys (Klenerman et al. 1980). After a two hour tourniquet application, the return to baseline pH took between 13 minutes (Shaw-Wiglis 1971) and 30 - 40 minutes (Modig et al. 1978, Klenerman et al. 1980).

Heppenstall and co-workers (1979) measured tissue pH using a Gore-Tex tube implanted in the muscle distal to the tourniquet. They showed a greater degree of acidosis in the tissues than in the blood, possibly because of the greater buffering capacity of blood. The tissue pH fell from a baseline of 7,40 to pH 7,0 after one hour, to a pH of 6,6 after two hours and to a pH of 6,5 after three hours. On release of the tourniquet, the rate of return to baseline pH levels was proportional to the duration of the tourniquet application, taking 15 - 20 minutes to normalise after a three hour tourniquet. A concomitant rise in tissue pCO_2 also occurred with maximal value of 75 mmHg after three hours' ischaemia.

Bicarbonate Concentration

In monkeys, tourniquet ischaemia caused the bicarbonate concentration to fall steadily until there was almost complete exhaustion of the buffer reserve after three hours. Three minutes after release of a two hour tourniquet, the bicarbonate and base excess reached their lowest mean values (Modig et al. 1978) and then followed the same time course of return to baseline as did the pH. Klenerman et

al. (1980) reported that the bicarbonate concentration took 20 minutes to return to control values after a three hour tourniquet.

These studies indicate that the acidosis caused by anaerobic metabolism in the ischaemic tissues increases with the duration of the tourniquet application. The pH of the blood in the ischaemic limb falls less than the pH of the tissues, probably due to its increased buffering capacity. However, the blood bicarbonate buffer reserve appears to be completely exhausted after three hours' tourniquet. The rate of recovery of the blood and tissue pH of the ischaemic limb to pre-tourniquet levels, is also proportional to the duration of the tourniquet application.

G. Oxygen Tensions

In Tissue

The PO_2 of a saline solution which is slowly perfused through a silastic tube implanted in the hindlimbs of a rabbit (method of Niinikowski and Hunt 1972) has been used as an indicator of tissue PO_2. Using this technique, Santavirta et al. (1976), found that the tissue PO_2 of rabbit muscle rendered ischaemic by three hour tourniquet applications, dropped to a minimum of 9 - 11 mmHg after 19 - 26 minutes and remained at this level for three hours. Tissue PO_2 returned to pre-tourniquet levels within 10 - 17 minutes, regardless of the length of tourniquet application. Tissue PO_2 rose rapidly when 100% O_2 was inhaled. The authors concluded that, even after three hours of tourniquet ischaemia, the micro-circulation

functioned normally. Similar conclusions were drawn from studies of humans (Romanus et al. 1978).

Heppenstall et al. (1979) implanted a Gore-Tex membrane (a tetrafluorocarbon tubular membrane) in the quadriceps of dogs and perfused it with hypoxic fluid to measure the pH and PO_2 of the effluent. After 20 minutes of tourniquet application, they reported that the tissue PO_2 was zero. The time taken to return to baseline PO_2 after tourniquet release depended on the tourniquet duration and was 10 minutes following one hours' ischaemia, 12 - 15 minutes after two hours' and 15 - 20 minutes after a three hours' ischaemia. They postulated that the delayed recovery of PO_2 due to arterio-venous shunting as well as to increased muscle oxygen consumption following tourniquet release. Similarly, Miller and coworkers (1978), used an implanted teflon diffusion membrane and showed that muscle PO_2 fell to very low levels of 3,0 mmHg after 1½ hours of tourniquet ischaemia. The return to control levels took 30 - 45 minutes after a 2½ hour tourniquet application.

In Blood

Shaw-Wilgis (1971) reported a marked fall in the venous PO_2 of the ischaemic limb from 45 mmHg to 4 mmHg after two hours of tourniquet application. The recovery time of PO_2 after removal of the tourniquet was dependent on the tourniquet time, and was 5 - 10 minutes after a one hour tourniquet, and more than 15 minutes after two hours. Déry et al. (1965) found the venous PO_2 to drop as low as 5

mmHg after only 25 minutes of tourniquet ischaemia. They also found a rapid return to baseline PO_2 levels within five minutes after 30 minutes' tourniquet ischaemia. Modig et al. (1978) reported that, in humans, venous PO_2 returned to pre-tourniquet levels within three minutes after tourniquet ischaemia.

Santavirta et al. (1978b) reported rapid equilibration between tissue and venous PO_2 even after a three hour tourniquet. However, others (Miller et al. 1978, Heppenstall et al. 1979) report that, even after only one hours' ischaemia, tissue gas tensions returned to pre-ischaemic levels more slowly than did the blood gas tensions.

Thus there is disagreement about the minimum values of tissue PO_2 reached during ischaemia and the speed of return of the PO_2 to pre-tourniquet levels. Some authors report a rapid return, even after three hours' tourniquet ischaemia, but most agree that the recovery time is proportional to the duration of tourniquet application.

H. Serum Potassium Levels

Klenerman and co-workers (1980) recorded a significant rise in potassium levels in the venous blood of the ischaemic limb during the tourniquet application. These levels reached a plateau between three and four hours but rose further if the duration of tourniquet application was increased to five hours. This corresponded to very large increases in the extracellular potassium concentration sur-

rounding ischaemic muscle cells found after three hours' ischaemia.

On release of the tourniquet, only transient and relatively insignificant rises in potassium levels in the systemic circulation have been found, presumably due to the large dilutional effect (Klenerman et al. 1980). The return of potassium levels to pre-tourniquet values in the venous blood draining the limb took 20 minutes after a tourniquet time of one hour, and 40 minutes after a tourniquet time of two to three hours (Klenerman et al. 1980). Others, (Déry et al. 1965, Modig et al. 1978), found a longer recovery time of some 30 - 60 minutes, after a tourniquet time of 60 minutes.

Using Xe 133 washout techniques, Larsson and Bergström (1978), found that after tourniquet release, the peak blood flow and venous potassium level in the ischaemic limb after tourniquet release occurred at the same time, reaching maximum values one to two minutes after release of a two hour tourniquet. Venous potassium levels in blood draining the previously ischaemic limb were still significantly raised 15 minutes after tourniquet release, but had returned to control values by 30 minutes. Jennische et al. (1982) found that although interstitial potassium levels fell rapidly in the first 15 minutes after release of a three hour tourniquet, they remained significantly elevated one hour later.

In summary, various authors have used venous potassium levels as an index of cell damage. After a tourniquet time of three hours, venous potassium levels take at least 30 - 40 minutes to return to control levels, whereas recovery of interstitial potassium levels takes even longer.

I. Serum Calcium Levels

Déry and co-workers (1965) reported a slight rise in serum total calcium levels, with a 10% fall in ionized calcium, in the ischaemic limb of monkeys after a 30 minute tourniquet application. Serum protein levels also increased. No explanation was offered for these calcium changes.

Tourniquet shock, caused by a five hour tourniquet application in dogs, is associated with marked rises in serum calcium levels in dogs (Stock and Isselhard 1972).

J. Serum Magnesium levels

Stock and Isselhard (1972) reported marked increases in serum magnesium in tourniquet-induced shock in dogs after mean tourniquet durations of five hours.

K. Muscle Enzyme Activities

Pääkkönen and co-workers (1981) performed muscle biopsies distal to the tourniquet in eight patients who underwent menisectomies with average tourniquet times of 65 minutes. Biopsies of the vastus

lateralis muscles were taken prior to the tourniquet application, just prior to tourniquet release, and again ten minutes and three days later. These samples were assayed for the activities of succinyl dehydrogenase (SDH), creatine kinase (CK), phosphofructokinase (PFK), malate dehydrogenase (MDH) and lactic dehydrogenase (LDH).

They reported that muscle enzyme activities were unaltered during ischaemia, but ten minutes after tourniquet release, the SDH and CK activities were significantly lower, whereas PFK, MDH and LDH activities were unchanged. By the third post-operative day, the CK, SDH, PFK and MDH activities were all lower and only LDH activity remained unchanged. SDH activity in the control limb also fell, probably reflecting a reduction in general physical activity in the initial post-operative period. Other workers, found no change in muscle SDH activity after two hours' tourniquet in man (Tountas and Bergman 1977). In rabbits, LDH activities were significantly decreased after 3 - 4 hours' tourniquet ischaemia (Santavirta et al. 1978), possibly indicating that the tourniquet causes greater muscle damage in rabbits than in humans (Pääkkönen et al. 1981), or that rabbit muscle is less resistant to ischaemic damage than is human muscle.

These studies indicate that the early biochemical and enzymatic changes after tourniquet application are poorly documented. For example, the only two studies on succinyl dehydrogenase activity in

muscle after tourniquet application, have given conflicting results. Laboratory animals may also give results different from man, possibly because of large differences in the muscle mass exposed to the tourniquet and in the differing muscle fibre types.

L. Skeletal Muscle Electrolyte Changes

Muscle Magnesium Levels

Larsson and Bergström (1978) found no change in total magnesium content in muscle biopsies taken before and after two hours' tourniquet ischaemia.

Muscle Sodium Levels

Muscle sodium levels were unchanged either during or after a two hour tourniquet (Larsson and Bergström 1978). However, Enger et al. (1978) measured a 20% decrease in muscle membrane potential at the end of a three hour tourniquet application. This should have caused a 30 - 40% increase of intracellular sodium concentration. However they measured only a small rise in muscle sodium, reaching maximum levels in the first minute after tourniquet release. No explanation was offered as to why this rise was of such a low magnitude.

Summary of Metabolic and Biochemical Changes

The application of a tourniquet for longer than 30 - 60 minutes has pronounced effects on various metabolic and biochemical parameters measured in the ischaemic tissue. Hypoxia, shown by decreasing PO_2

levels, stimulates anaerobic glycolysis which increases muscle lactate levels, decreases muscle glycogen stores and increases hydrogen ion concentration. Eventually the decrease in pH exhausts the tissue and blood buffer reserves and interferes with cellular function, in particular the production of ATP. Once adenosine triphosphate stores are depleted, normal cellular functioning is impaired and the membrane potential falls as potassium leaves and sodium enters the cells. With more prolonged hypoxia, possibly in conjunction with direct damage caused by the tourniquet pressure, intracellular enzymes such as creatine kinase, are released into the serum.

Intermittent release of the tourniquet for 10 - 15 minutes every hour appears to decrease these adverse metabolic changes. Thus metabolic changes after a three hour tourniquet time are reported to be similar to those found after only a one hour application.

2.6 VASCULAR CHANGES

A. Haemodynamic Changes

During the Tourniquet Application

Klenerman and Crawley (1977) investigated the hypothesis that, despite the application of a tourniquet to the upper or lower limb, blood flow may persist via intramedullary canals (Furlow 1971, Spira et al. 1965). Using small microspheres labelled with 51 chromium and measuring tissue washout of 22 sodium, they showed that blood flow in the tourniquet limb was less than 1% of the flow

to the control limb. They concluded that intramedullary canals are not physiologically significant.

Romanus and co-workers (1978) used intravital microscopy to study the microcirculation in man during and after ischaemia. They found that during one and two hours of ischaemia, the trapped blood cells did not stick to each other or to the vascular walls, although some red blood cells tended towards rouleaux formation. After six hours of ischaemia, some red blood cells had formed homogenous masses indicating haemolysis; diapedeses of red blood corpuscles was also noted and there were signs of increased white blood cell stickiness.

Immediately After Tourniquet Removal

Post-tourniquet Hyperaemia

The pronounced increase in blood flow, after release of the tourniquet, has been ascribed to various mechanisms :

(a) Increased levels of carbon dioxide, hydrogen ions, potassium, magnesium, lactate and pyruvate.

(b) Reduced phosphagen stores of the vessel wall (Stock and Isselhard 1972).

(c) Increased levels of other metabolites.

(d) Increased blood osmolarity, which causes relaxation of vascular smooth muscle (Mellander et al. 1967).

Larsson and Bergström (1978) reported that venous osmolarity increased 16 mosm/Kg H_2O, one to two minutes after removal of the tourniquet. The increase in potassium, lactate and sodium levels accounted for 12 mosmoles and the remainder was due to moderate increases in glucose and calcium levels. The increased osmolarity was maximum one to two minutes after tourniquet release and this coincided with the maximal blood flow as measured by Xenon 133 washout. Similar rises in osmolarity have been reported after soft tissue trauma to dogs' hind limbs (Sandegard et al. 1974).

Using intravital microscopy, Romanus et al. (1978) demonstrated that circulation had returned to all vessels within seconds after release of a one to two hour tourniquet. The hyperaemic reaction lasted for about 30 minutes. There was also an early increase in the number of white blood cells sticking to the vascular walls but no thrombus formation or red blood cell diapedesis was seen. After a three to six hour ischaemic period, reflow occurred in all vessels but was delayed for several minutes. Microthrombi were seen in one experiment, as well as marked white blood cell stickiness, red blood cell diapedesis and homogenous masses of red blood cells which slowed the re-perfusion rate. The longer ischaemic period also caused more marked oedema and endothelial damage.

Delayed Changes After Tourniquet Release

The hyperaemic period may end if there is excessive accumulation of oedema (Strock and Majno 1969, Miller et al. 1979). Strock and

Majno (1969) noted a marked difference in the amount of skin and muscle oedema caused by a tourniquet application. The skin appeared to accumulate more water than did the other tissues after a tourniquet time of as little as 30 minutes. This suggested that the hyperaemic response would be decreased, first in the skin and only then in the other tissues.

Larsson and Lewis, 1978 used double-isotope-clearance techniques in 25 patients who underwent knee surgery under tourniquet. They showed a smaller and later initial increase in blood flow on tourniquet release, when the tourniquet time exceeded 60 minutes. Nine of 16 legs showed a maximal transport function only one to two days post-operatively.

Using intravital microscopy techniques, Romanus and co-workers (1978), examined the microcirculation of two subjects, 24 hours after six hours' tourniquet ischaemia. In one subject there was complete circulatory standstill whilst blood flow in the other was almost normal. These authors were unable to explain this difference and concluded that the final outcome of the six hour ischaemic insult remained uncertain.

B. THE BLOOD CLOTTING SYSTEM

The Fibrinolytic System

The fibrinolytic system appears to be stimulated by tourniquet application (Nakahara and Sakahashi 1967), perhaps due to release of plasminogen activators from the vasa vasorum (Klenerman and

Crawley 1977). Thus, operations involving tourniquets appear to be associated with a lower incidence of deep venous thrombosis (Klenerman and Crawley 1977, Fahmy and Patel 1981, Kroese and Stiris 1976, Simon et al. 1982). This effect on fibrinolytic activity has even been used with some success to prevent deep lower limb venous thromboses by using intermittent compression of the arms (Knight and Dawson 1976). A five hour tourniquet on dogs' hind limbs produced the appearance of deep-vein thrombosis in several of the 30 experimental animals which were divided into varying groups to assess the efficacy of heparin or low molecular weight dextran (Rhea and Foster 1961). Dextran given 30 minutes prior to tourniquet removal appeared to prevent the occurrence of the deep vein thrombosis. Heparin (3mg/Kg) intravenously 30 minutes prior to tourniquet release was also reported to decrease the subsequent limb-oedema and swelling by almost 50%. However, other authors (Price et al. 1980) contend that in clinical practice the incidence of deep vein thrombosis after operations under tourniquet is no less than other lower limb procedures such as hip replacements (in which a tourniquet is not used).

The possibility exists that this elevated fibrinolytic activity might be more likely to cause post-operative bleeding (Miller et al. 1979). For this reason, Newman and co-workers (1979) have suggested that a tourniquet should not be removed until a firm occlusive bandage had been applied. They reported that 400 ml more blood was lost when the tourniquet was removed prior to wound

closure, than when it was removed after closure. However, these patients had also been on low dose heparin as prophylaxis against deep vein thrombosis development, so their clotting ability may have been impaired. In contrast, Klenerman (1982) recommends early release of the tourniquet. He points out that if the tourniquet is released before wound closure, the blood loss is more readily measured and replaced while the patient is still in the operating theatre. However, if the tourniquet is left inflated until all the dressings and plaster have been applied, the patient may subsequently collapse because of an unrecognized 'hidden' blood loss.

Pre-treatment of monkeys with heparin prior to tourniquet application prevented the consumption of fibrinogen and antithrombin III, but did not prevent an elevation of fibrin split products (Larsson and Risberg 1977, Risberg 1977). This suggested that non plasmin fibrinolytic agents, such as proteinases released by polymorphonuclear leukocytes, may be important in increasing fibrinolytic activity. Increased plasminogen activity has been found in the blood draining the lower limbs during tourniquet ischaemia (Larsson and Risberg 1977, Fahmy and Patel 1981). The return of fibrinogen, antithrombin III and fibrin split products to pre-ischaemic levels took five minutes after tourniquet deflation. But fibrinolytic activity may be increased for up to 15 - 30 minutes after tourniquet release (Fahmy and Patel 1981, Klenerman and Crawley, 1977).

Platelet Aggregation

Stebhens and Biscoe (1967) described hydropic inclusion bodies in platelets, erythrocytes and endothelial cells during ischaemia. They postulated that these inclusion bodies may release adenosine diphosphate which would cause increased platelet aggregation after tourniquet application.

Romanus and co-workers (1978), however, found no thrombus formation in the microcirculation after one or two hours' ischaemia, although a six hour ischaemic period did produce a small adherent platelet thrombus in one subject.

Zahavi et al. (1980) measured plasma thromboglobulin, a marker of in-vivo platelet reaction and plasma thromboxane B_2, a stable product of thromboxane synthetase. They found an increase in both activities 15 - 30 minutes after tourniquet ischaemia in humans. In pig experiments they also showed reduced prostacyclin activity in blood draining from the ischaemic limb when compared to that from the control limb. When examined under a scanning electron microscope the veins of the ischaemic pig limb showed large de-endothelialised areas covered with a monolayer of platelets and platelet clumps. However, these results may be animal specific as other workers (Strock and Majno with rats 1969, Solonen and Hjelt 1968 and J'ozsa et al. 1980 with humans) have not reported similar endothelial damage or platelet layering. Zahavi et al. (1980) considered their results may explain the high incidence of venous

thrombosis affecting patients undergoing menisectomy and total knee replacement under tourniquet ischaemia. However, as already stated, a decreased incidence of deep vein thrombosis after operations involving the use of a tourniquet has been reported by the majority of workers. (See The Fibrinolytic System)

Chen et al. (1982) found marked differences in platelet adhesiveness, thromboxane A2 and prostacyclin activity, between healthy subjects and patients with known ischaemic heart disease, after tourniquet application. Tourniquet application in healthy subjects induced a significant increase in prostacyclin generation; a similar increase was not seen in ischaemic heart disease patients, whereas both groups had increased thromboxane A_2 levels. This finding suggests that patients with ischaemic heart disease may be more prone to developing platelet venous thromboses after a tourniquet application. This correlation has not been reported in the literature but could help to explain the reported differences in the incidence of deep vein thrombosis after tourniquet application.

An increase in prostacyclin and fibrinolytic activity, in non-atherosclerotic subjects, would also help explain the findings of Romanus et al. (1978). Using intravital microscopy techniques, they found only one platelet thrombus after six hours' ischaemia in healthy medical students.

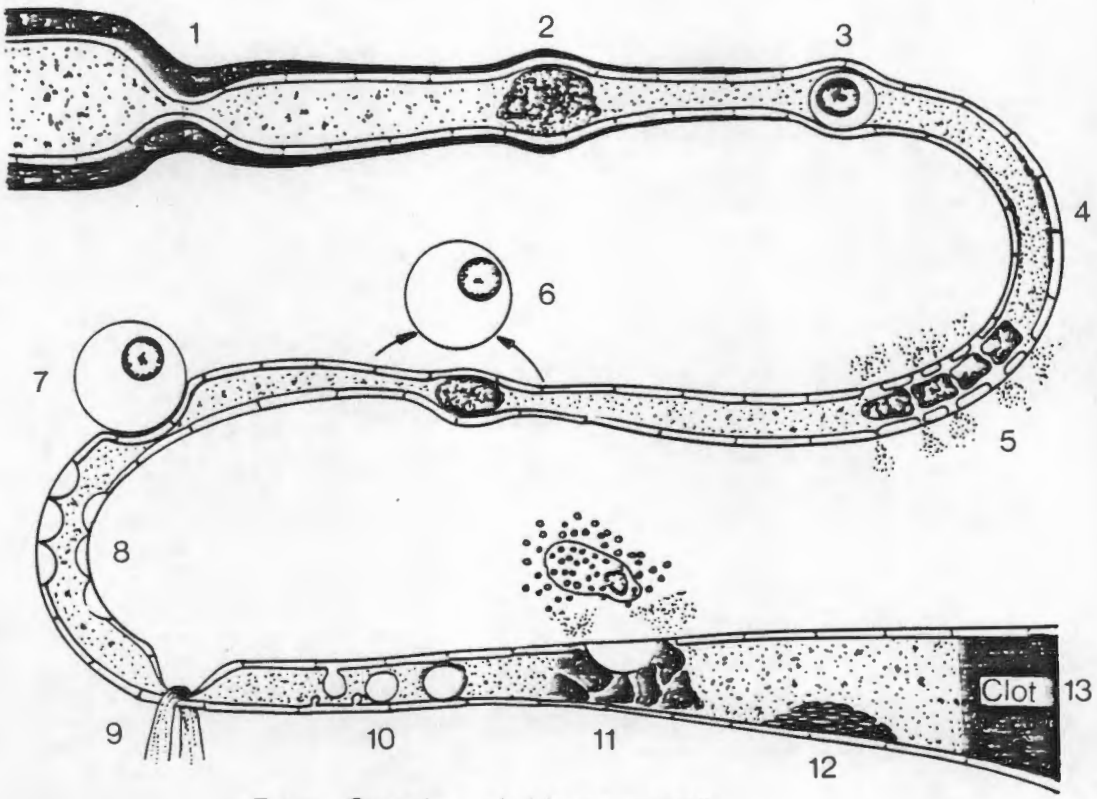
C. The No-Reflow Hypothesis

The no-reflow phenomenon after tourniquet application was first hypothesised by Strock and Majno (1969a). They studied rats who had had a tourniquet applied to a limb. Injecting carbon black into the tail vein at the release of the tourniquet, they demonstrated that some vessels in the limb remained occluded for a considerable period of time, even after a 15 minute tourniquet application. After tourniquet times of 2½ hours, only the major blood vessels were found to be patent immediately after tourniquet release. After a further two hours' "recovery", the carbon was deposited equally in both limbs, indicating the blood flow to the muscles of the ischaemic limb and control limb were the same. In a later article they listed thirteen possible causes for this temporary, functional obstruction (Strock and Majno 1969) (Fig. 2:1).

Miller et al. (1979) reported that the tissues distal to the tourniquet site were oedematous on removal of the tourniquet. This increase in tissue pressure may be involved in the "no-reflow phenomenon" as Ashton (1975) reports that : (1) Active closure of arterioles occur when transmural pressure is lowered, and (2) Passive collapse of capillary walls occurs when tissue pressure is greater than intraluminal pressure.

FIGURE 2.1

THE NO REFLOW HYPOTHESIS



From: Strock and Majno., 1969.

From : Strock and Majno, 1969(b)
(Publication Permission Applied For)

1. Arteriolar spasm
2. Impaction of microemboli
3. Anoxic-ischaemic swelling of trapped white blood cells
4. Alterations of endothelial surfaces causing stickiness
5. Direct injury to endothelial cells with fragmentation, formation of gaps, loss of fluid and stasis
6. Loss of fluid to perivascular cells
7. Compression by swollen perivascular cells
8. Endothelial swelling
9. Collagen swelling constricting the vessel
10. Intramuscular blebs arising from the endothelium
11. Formation of histamine leaks due to mast cell damage
12. Formation of platelet thrombi
13. Intravascular clotting

It has been postulated that the no-reflow phenomenon may explain the delayed rise in CK activity in the venous blood after a two hour tourniquet time (Chiu et al. 1976, Heppenstall et al. 1979). Using this index, Chiu and co-workers (1976) suggest that the no-reflow period lasts one hour after a two hour tourniquet time. Similarly, the delay in equilibration between the serum and interstitial potassium levels may be partially explained by the no-reflow phenomenon (Jennische et al. 1982). This delay in equilibration took more than an hour after a three hour tourniquet application to rabbit hind legs.

Larsson and Bergstrom (1978) also described an apparent post-tourniquet no-reflow phenomenon in the muscles of rat limbs; the skin appearing to be less affected than skeletal muscles.

Summary of Vascular Changes

The application of a tourniquet effectively prevents any blood flowing into the limb. Thus the blood remaining in the ischaemic limb is subjected to progressive hypoxia. This causes changes in the platelets, red blood cells and endothelium which renders thrombus formation more likely. The formation of platelet thrombi has not been clearly documented after tourniquet durations of up to three hours. However, many clotting parameters are species- and disease-specific so that pigs and patients with ischaemic heart disease may have an increased propensity to form platelet clumps after tourniquet ischaemia when compared with dogs or healthy patients. This, together with fibrinolytic changes, could explain the reported differences in the incidence of deep vein thromboses after operations under tourniquet. Any no-reflow phenomenon would also be more severe if platelet clotting is activated and this would prolong the duration of anoxia.

Several mechanisms have been postulated to explain reactive hyperaemia which occurs after tourniquet release. Strock and Majno (1969b), however, maintain that some vessels supplying the tissue remain occluded for a period of time after tourniquet release; the occlusion time being proportional to the tourniquet duration.

Oedema and tissue swelling are common in the hours after tourniquet release, the skin appearing to accumulate more water than the muscles. Post-operative tissue bleeding, caused by activation of the fibrinolytic system during tourniquet application, has also

been suggested as a potential cause of post-operative complications.

2.7. SKIN TEMPERATURE CHANGES

Skin temperatures have been measured by several authors (Sanders 1973, Modig et al. 1978, Déry et al. 1965, Harris et al. 1975). They all note a tendency for the temperature of the ischaemic limb to fall towards room temperature during the tourniquet application. Some (Strock and Majno with rats, 1969a) recorded very rapid drops to a low plateau over the first hour. Others (Modig et al. with humans, 1978) recorded a more gradual decline in temperature, perhaps an indication of the larger mass of the limb which has to equilbrate with the external temperature. As would be expected with actively metabolising tissue, the temperature never drops to that of room temperature, even when the animals were studied in an incubator at 28°C (Strock and Majno 1969).

On release of the tourniquet, the skin temperature rises rapidly to a plateau within four to eight minutes (Modig et al. 1978, Déry et al. 1965). In Modig and co-workers' report (1978), there was a tendency, not statistically significant, for the thigh and calf skin temperatures to exceed the pre-ischaemic levels. Sanders (1973) reported that the skin temperature of arms of patients who had undergone a one hour tourniquet application, rose 1.5°C above pre-operative levels on tourniquet release.

In contrast, Strock and Majno (1969a) reported that the temperature of the ischaemic limb remained about 2°C lower than that of the control limb after release of a two hour tourniquet in rats. They postulated that this could be due to decreased cellular metabolism, increased heat loss by the oedematous tissue, decreased blood flow, or any combination of these.

In summary, skin temperatures of the ischaemic limb have been shown to fall during tourniquet application. The different rates of fall may be due to the differing muscle masses of the animals studied. On release of the tourniquet, the skin temperature rapidly rises to pre-tourniquet levels. In some reports there is a tendency for this temperature to exceed pre-ischaemic levels, but this is not substantiated by others. Muscle temperatures do not appear to have been monitored in the tourniquet experiments described.

2.8 COMPLICATIONS REPORTED WITH USE OF THE TOURNIQUET

A. Neurological

One of the major complications of tourniquet application is that of paralysis and paresis. The prevalence and possible mechanisms involved have already been discussed. (Chapter 2.4)

B. Systemic Complications

Central Venous and Mean Arterial Pressure Changes

Bradford (1969) measured a rise in central venous pressure (CVP) of some 17,5 cm H_2O if both legs were exsanguinated prior to the application of bilateral leg tourniquets. If one leg only was

exsanguinated, the rise was 9,7 cm H_2O. Without exsanguination, no change in central venous pressure occurred on application or release of the tourniquet. The auto-transfusion of 700 - 800 ml of blood from each leg on exsanguination is believed to cause these changes. With exsanguination and a tourniquet applied to one leg, the mean arterial pressure rose by 18,5 mmHg and on release it fell by 19,1 mmHg, due to changes in peripheral resistance.

Care is necessary, therefore, when a limb tourniquet is applied to a patient who has mild congestive cardiac failure, in case auto-transfusion causes a rapid rise in central venous pressure which could precipitate or exacerbate cardiac failure (Sanders 1973). This was perhaps the cause of the cardiac arrest shortly after the aplication of bilateral leg tourniquets reported in Middleton and Varian's survey (1974).

Hypertension

In a review of 600 patients who had had a tourniquet applied to a lower limb, Kaufman and Walts (1982) found that the incidence of induced hypertension was 11%. The probability of hypertension (defined as a 30% increase on pre-tourniquet blood pressure levels) was increased if the patient was elderly, had cardiac enlargement, or had a nitrous oxide or narcotic anaesthesia. By comparison, the incidence of hypertension in a control group of 100 patients undergoing hip surgery without a tourniquet was one percent.

Pulmonary microemboli

Edfeldt and Thomson (1980) reported that, upon release of the thigh tourniquet in 26 patients operated upon for osteoarthrosis of the knee, cardiac output and arterial PO_2 decreased, implying pulmonary microembolism. It was suggested that liberation of tissue thromboplastins, causing aggregation of thrombocytes and trapping of fibrin, and not the release of particles of the acrylic monomer used with the prosthesis, caused these microemboli. These authors felt that pre-treatment with steroids could have a beneficial effect in preventing microemboli formation in patients with fractures undergoing operations under tourniquet.

This is supported by the findings of Modig et al. (1978) who investigated pulmonary and circulatory changes in total hip replacements, in which the potential risk of acrylic monomer microembolization was studied. Pre-treatment of patients with large doses of steroids (30 mg/Kg methylprednisolone) prevented the fall in cardiac output and improved the leg and pulmonary blood flow.

Pulmonary Embolism

The incidence of deep vein thrombosis appears to be decreased by the use of the tourniquet (Chapter 2.5B). However, some patients who are to have tourniquets applied for reparative surgery have been immobilised in bed prior to their operations. These patients have a high potential for the development of a deep vein thrombosis during immobilization. Austin (1963) reported two cases and Estrera et al. (1982) one case who suffered from a pulmonary

embolism. These emboli were thought to be due to the dislodgement of a preformed clot from the femoral vein, during the application of an exsanguinating bandage. Although the patient of Estrera et al. (1982) was successfully resuscitated, the two patients reported by Austin (1963) died and at post mortem showed extensive antemortem thrombi in the veins of the injured leg. These thrombi had been clinically silent at the time of surgery.

Other Systemic Changes

Other systemic effects occurring on release of the tourniquet, appear to be mild and transient (Modig et al. 1978, Shaw-Wiglis 1971, Klenerman et al. 1980, Hurst et al. 1981).

C. ARTERIAL DAMAGE

Plaque Disruption

There is the possibility of disruption of an atheromatous plaque causing occlusion of the superficial femoral artery under the tourniquet. Thus Giannestras et al. (1977), suggest that an emergency arteriogram and perhaps arteriotomy, should be performed if the limb circulation does not return rapidly to normal after removal of a tourniquet.

Aneurysm Formation

Webb Jones (1955) and Scott (1955) reported aneurysms which occurred after foot operations, but they occurred secondary to unrecognized trauma of the exsanguinated arteries. All the above cases had had tourniquets applied to the thigh.

Volkmann's Ischaemic Contracture

Cases of Volkmann's ischaemic contracture and even gangrene due to "arterial spasm" have been described after the use of Esmarch's bandages and solid rubber bands as tourniquets (Wallis 1901, Griffiths 1950, Watson-Jones 1952). Barnes and Trueta (1942) were able to produce long-standing arterial spasm in rabbits when they used tourniquets consisting of a soft wire encased in rubber tubing. With soft tubing alone, this spasm did not occur. Today, Volkmann's ischaemic contracture is more likely to occur when too tight a dressing or plaster is applied to a limb, or when there is marked swelling after tourniquet release.

The Post-ischaemic Hand Syndrome

The post-ischaemic hand syndrome of oedema, colour changes, paresthesia and weakness, occurs particularly in subjects who have an impaired circulation prior to tourniquet application (Tubiana 1973).

D. COMPLICATIONS ASSOCIATED WITH SPECIFIC DISEASES

Monckeberg's Calcinosis

Calcification of the arteries, in a reported case of Monckeberg's calcinosis, caused the tourniquet to act as a venous tourniquet as the artery could not be occluded. Hence, when the tourniquet was pressurised, the bleeding at the operative site actually increased (Jeyaseelan 1981).

Sickle Cell Disease

An estimated 8 - 14% of the American Black population have sickle cell haemoglobinopathy and are prone to undergo sickling, thromboses and tissue infarction if subjected to hypoxia. These are theoretical reasons why tourniquets are avoided in this population group. Stein and Urbaniak (1980) undertook a 17-year review of tourniquet procedures which involved 29 tourniquet applications to 21 patients with sickle cell disease. They found no differences between the incidence of complications in the sickle cell patients and that in a randomly selected normal control population. They concluded that the use of the tourniquet was not contra-indicated in patients with sickle cell disease.

E. OEDEMA

Swelling of the hand occurs within ten minutes of the release of an arm tourniquet under normothermic conditions (Paletta et al. 1961). It is usually maximum at two hours and persists for up to a week (Lundborg 1970). The oedema appears even after a tourniquet time as short as one hour (Stock et al. 1971, Heppenstall et al. 1979) and can seriously hinder tissue healing. To minimise the swelling, Sanders (1973) recommends elevation of the upper limb for at least five days after surgery using the tourniquet.

Miller and co-workers (1979) suggested that post-tourniquet oedema was the cause of the significantly higher pressures measured in both the vastus lateralis and anterior tibial muscles of primates 24 hours after a 2½ hour tourniquet. They noted that this pressure

rise may cause compartmental syndromes in those muscle groups bounded by rigid fascial sheaths.

Larsson and Bergstrom (1978) showed that the increase in total muscle water which occurred within one minute of tourniquet release was mainly due to increased extracellular water. Morphological studies by several authors (Harman 1947, Heppenstall et al. 1979, Solonen and Hjelt 1968, J'osza et al. 1980) confirmed this.

F. TOURNIQUET SHOCK

Tourniquet shock, caused by the release of a very prolonged tourniquet application, is a well described entity (Stock and Isselhard 1972, Stock et al. 1975, Kristen et al. 1970, Schubert et al. 1976). The removal of a five hour tourniquet from the hind limb of dogs caused an immediate fall in blood pressure, and led to renal failure (Stock and Isselhard 1972). These authors suggested that circulatory collapse was caused by the marked vasodilation and oedema in the ischaemic limb due, in part, to ATP depletion in the smooth muscle of the blood vessels. Kirsten and co-workers (1970) suggested that the profound release of potassium from the damaged muscle cells after tourniquet release was the probable cause of early cardiac arrest in many of the dogs.

G. OTHER COMPLICATIONS

Using a retrospective questionnaire study completed by 151 responding orthopaedic surgeons, Middleton and Varian (1974) reported the following complications associated with the use of a tourniquet :

one case of full thickness burns from a 'hot' tourniquet; one femoral artery 'spasm' with full recovery; two cases of post-operative intermittent claudication, one of which required by-pass surgery; one case of Volkmann's ischaemic contracture, and one case of sudden cardiac arrest after bilateral leg exsanguination.

Flatt (1972) reported the case of a full circumferential burn caused by the alcohol skin cleaning solution soaking the tourniquet.

SUMMARY OF AND RECOMMENDED PRECAUTIONS TO DECREASE THE CLINICAL COMPLICATIONS ASSOCIATED WITH TOURNIQUET USE

Many complications of tourniquet application are listed in the literature. Some, such as dislodgement of an atheromatous plaque, or aneurysm formation, are extremely rare. Others, such as an increase in mean arterial and central venous pressures, occur frequently with limb exsanguination prior to tourniquet application. Swelling of the limb due to oedema or vascular insufficiency, after tourniquet release, can lead to the serious complications of post-ischaemic hand syndrome or Volkmann's ischaemic contracture.

In order to reduce the frequency of some of the complications, various recommendations have been made:

Logel (1976) reported a case of a rupture of the long tendon of biceps brachi muscle after an operation utilising an arm tourniquet. However, other factors, such as rheumatoid arthritis and

local corticosteroid injections, also probably accounted for a decrease in tensile strength of the tendon and these, together with the ischaemia and pressure created by the tourniquet, led to the tendon's subsequent rupture.

(a) The Patient

Klenerman (1982) has recommended that, prior to the use of an above knee tourniquet, especially in elderly patients, the state of the skin and nails and presence of hair in the limb should be noted. One pedal pulse, preferably the posterior tibial, should be palpable. Radiographs of the knee should also be checked for evidence of calcification of the vessels. Patients who have anaemia, hypovolaemia, metabolic acidosis or pre-existing cardiovascular disease have a reduced buffering capacity. Thus, special care should be taken with these patients because of the risk of sudden cardiac collapse on removal of the tourniquet. Care should also be taken to avoid using a tourniquet on subjects who may already have a deep vein thrombosis because of the risk of pulmonary embolus.

Klenerman (1982) and Rorabeck (1980) recommend that the shape and size of the patient's limb be taken into account when estimating the tourniquet pressure to be applied.

(b) The Equipment

The automatic tourniquet apparatus should be checked regularly for accuracy and stability (Chapter 5.5).

Additional towelling should be placed over the tourniquet to mop up any excess skin preparation fluid. The towel should be removed prior to inflation of the cuff (Flatt 1972).

(c) Patient After-care

If possible, the upper limb should be elevated for at least five days after surgery under tourniquet (Sanders 1973). Dressings and plaster should be sufficiently loose to allow for post-operative limb swelling. The dressings should be carefully checked for tightness in the early post-operative period in order to prevent ischaemic damage to the tissues.

2.9 OVERALL SUMMARY AND CONCLUSIONS ON THE EFFECTS OF TOURNIQUET APPLICATION

In a general way, the following can be said:

Although the tourniquet has been used for several centuries, the pneumatic tourniquet only came into clinical use in 1904. Since then it has been used extensively in various limb operations for which the surgeon requires a bloodless field. However, there is still much debate as to the amount of damage caused by its application and its safe pressure or duration. Although morphological damage to skeletal muscle appears to be minimal in the first hour of tourniquet application, capillary endothelial damage and oedema occurs within the first 30 minutes.

Neurological tissue appears to be much more sensitive to the shear forces exerted under the edge of a tourniquet than to ischaemia or

direct pressure alone. The high reported incidence of electromyographically proven partial denervation of the skeletal muscles after tourniquet application has important implications for the sportsman undergoing surgery. Full rehabilitation of a muscle which has a defective nerve supply will never be achieved until the nerve has regenerated, a process which may take three to six months. Thus, in future, the injured sportsman wishing to return to his sport as soon as possible may well be advised to ask the surgeon to avoid the use of the tourniquet, if at all possible.

The metabolic effects of anoxia are pronounced within 30 - 60 minutes of tourniquet ischaemia and increase with the duration of its application. The exhaustion of energy-rich phosphate stores occurs after about three hours of tourniquet application, after which time the various metabolic and energy requiring cycles of the tissue cells begin to fail. It would thus seem that prolonging the tourniquet duration longer than three hours would severely damage the integrity of the ischaemic tissue. One way of preventing the total exhaustion of adenosine triphosphate is to release the cuff for 10 - 15 minutes every hour. Another way would be to attempt to slow the cells' metabolic rate during the ischaemic period.

The reactive hyperaemia after tourniquet release has long been recognised. However, it appears that, after two hours' tourniquet, a no-reflow phenomenon may occur. This implies that certain areas, distal to the tourniquet, may remain ischaemic and, therefore, liable to continued damage for up to an hour after release of a two

hour tourniquet. Whether this is due to temporary platelet plugging because of increased platelet aggregation or whether it is a purely functional cause, has not been elucidated. Also unclear is whether or not the application of a tourniquet causes an increased or decreased risk of deep vein thromboses.

Thus, whilst the complications of the actual procedure are formidable, some of the precautions to decrease them in clinical practice are relatively straightforward. I believe that the use of the tourniquet can be made safer if the surgical team is made aware of its problems and can learn to avoid them.

CHAPTER THREE

A REVIEW OF THE LITERATURE ON THE EFFECTS AND USE OF LOCAL AND WHOLE BODY HYPOTHERMIA

3.1 HISTORICAL BACKGROUND

The use of cold as a therapeutic modality has its origins in antiquity. Hippocrates used cold application in 300 B.C. and noted that it decreased swelling and reduced pain by producing numbness. In 1661 Thomas Bartolin wrote a treatise on the medical uses of snow in leg resections, ulcer cautery and perineal lithotomy incisions for bladder stones. Larrey, chief surgeon to Napoleon, used refrigeration anaesthesia for amputations on the Russian Front in 1813 (McMaster 1982).

Total body hypothermia was described in 1862 by Walther who reported the effects of cooling rabbits to 20°C. Smith and Fay (1940) produced body temperatures of 29 - 35°C for four to five days in the treatment of cancer patients. In 1950, Bigelow and co-workers in Canada reported the first use of hypothermia during cardiac surgery. Since that time the use of hypothermia, by extracorporeal blood cooling, has continued to play an important role in open heart surgery, as well as in certain neurological operations. Various workers have also reported the protective effect of hypothermia in experimentally induced haemorrhagic shock (Postel et al. 1957, Stock et al. 1975, Haljamäë et al. 1970, Hagberg et al. 1970).

3.2 THE PHYSIOLOGICAL AND BIOCHEMICAL EFFECTS OF HYPOTHERMIA

Most of the physiological and biochemical effects of hypothermia have been described for total body hypothermia. Andjus and co-workers (1956) succeeded in cooling rats to 0°C and below. The lowest temperature they obtained, with subsequent survival, was -5°C and this temperature was maintained for as long as 70 minutes. This suggests that the

achievement of almost zero oxygen consumption with recovery is possible in warm-blooded animals.

A. Tissue Oxygen Consumption

Oxygen uptake decreases as temperature falls (Abrahamson et al 1958) although, as Gray and Nunn (1980) point out, this does not necessarily indicate a lowered oxygen requirement. There is a leftward shift of the haemoglobin dissociation curve so that oxygen is less easily released to the tissues. This shift, however, may not affect oxygen utilisation by the tissues because of increased oxygen solubility at low temperatures (Lundsgaard-Hansen 1966).

B. Blood Acid Base Balance

The acid base balance appears to be relatively unaffected by hypothermia, provided no crisis occurred on rewarming, and there was no passive congestion (Lundsgaard-Hansen 1966). If either occurred, a metabolic accidosis results. All pH readings taken at a low body temperature must be corrected to that body temperature if the pH meter has been calibrated to read at 37°C.

C. Basal Metabolic Rate

Basal metabolic rate falls with the fall in body temperature, if shivering is prevented. Some animal studies have suggested that, when the body temperature falls below 10 - 15°C, metabolism has essentially stopped (Lynn et al. 1954). This has been disputed by others who believe cellular metabolism persists even at these low temperatures (Benazon 1960).

D. Tissue Carbohydrate Metabolism

Hypothermia is believed to interfere with the enzymes regulating glucose metabolism (Wynn 1956). Blood glucose rises due to decreased insulin release and reduced liver glucose uptake. This mild degree of hyperglycaemia may cause a degree of cellular dehydration (Wynn 1956).

E. Changes in Blood Flow, Blood Viscosity and Blood Coagulability

Blood flow decreased slightly in a limb immersed in a water bath at 13 - 15°C for two hours, although the reduction in flow was only conspicuous during the first 15 minutes (Barcroft and Edholm 1943).

Blood viscosity increases as the temperature falls and sludging in the capillaries may occur. There is thrombocytopaenia, haemoconcentration and a reduction in the eosinophil and leucocyte counts. The coagulation processes are also markedly slowed and, during prolonged cooling, there is a progressive loss of fibrinogen due to the release of fibrinolysins (Gray and Nunn 1980). This has led to occasional bleeding problems during extracorporeal blood cooling used in cardiac by-pass surgery.

F. Serum Electrolyte Changes

With whole body cooling in normovolaemic patients and animals, there is a significant rise in serum potassium. This is further increased if a metabolic acidosis occurs or if there is an infusion of stored blood (Wylie and Churchill-Davidson, 1972).

Hypothermia has been shown to influence serum potassium levels after haemorrhagic shock. Haljamäë (1970) and Hagberg et al. (1970) showed that when haemorrhagic shock developed under normothermic conditions, the potassium content of the cells was markedly lowered and no active cellular potassium reaccumulation was seen. However, when haemorrhagic shock was treated with hypothermia, the initial intracellular potassium loss was less, and active re-accumulation occurred during recovery (Haljamäë, 1970). In these animals there was also only a moderate increase in the potassium content of the local tissue fluid and only a slight increase in plasma potassium concentrations. The corresponding changes in the normothermic, shocked animals were much greater.

G. Neuromuscular Function Effects

Muscle cooling below 20°C delays twitch time and the tension produced during muscular contraction. Neuromuscular transmission at the end plate is decreased below 15°C and totally blocked at 5°C. However, motor end plate potentials are shown to persist down to 1°C (McMaster 1982).

3.3 LOCAL HYPOTHERMIA AND TOURNIQUET APPLICATION

There are very few studies of the use of hypothermia during tourniquet application.

Paletta et al. (1961) cooled the limbs of dogs prior to and during tourniquet application. When compared to the normothermic limbs, there was less histological damage, a more rapid hyperaemia and the suggestion of

an increased blood flow in the cooled limbs after tourniquet release. Shehardi et al. (1961) also reported that hypothermia reduced post-operative tourniquet paralysis and oedema in dogs.

The immersion of rats' tails in water at 0°C, during the application of a two hour tail tourniquet, inhibited the extent of the subsequent swelling, both during the early period and during the first week after tourniquet removal (Rosenthal and Thornton, 1970). Exposure of the tail to 37°C during this period caused a marked and prolonged swelling; tail volume increasing over a period of 15 days to 163% of the original. Cooling or warming of the tail (0°and 15°C) after tourniquet removal had no significant effect upon the course of the swelling.

Nakahara and Sakahasi (1967) found a marked decrease in the post tourniquet bleeding tendency in an experiment where the limb was cooled by 10°C prior to tourniquet application. They also presented four cases in which pre-cooling of the lower limbs by 10°C before tourniquet application resulted in a consistent decrease in post-operative complications.

A similar technique was reported by Seki (1980) who cooled the forearm with ice bags for 30 minutes after induction of general anaesthesia and before tourniquet application. In 12 cases in whom a tourniquet was kept inflated for an average of 3½ hours (maximum time : 4 hours, 7 minutes), the only complications were temporary dysaesthesia at the finger tips in two cases and a tingling in the fingers when the wrist was tapped (Tinnel's sign) in another. The same author also performed an experimental study on 35 dogs in which tourniquets were applied for five hours after

the limb had been cooled from 38°C to 16 -18°C by immersion in ice. Oedema was reported to subside much faster in the cooled group, who also stopped limping faster than did the control group.

3.4 CONTRA-INDICATIONS TO THE USE OF HYPOTHERMIA

Patients in whom the use of hypothermia may be contra-indicated are those susceptible to cold-induced injury. Subjects with collagen diseases such as lupus erythematosis and rheumatoid arthritis may develop severe vascular spasm on cold exposure. Some patients exhibit a cold allergy caused by cold agglutinins and some develop cryoglobinuria or haemoglobinuria on cold exposure. Thus patients with an impaired peripheral circulation require careful assessment before the additional insult of hypothermia is considered.

3.5 SUMMARY AND CONCLUSION ON THE EFFECTS AND USE OF HYPOTHERMIA

Most of the physiological and biochemical changes that occur during hypothermia have been reported for whole body cooling of animals and humans. Hypothermia has been found to protect the body tissues and organs when the normal circulation is interrupted, as during cardiac surgery or in haemorrhagic shock. Some workers described the local use of hypothermia and tourniquets in dog experiments in the 1960s (Paletta et al. 1961, Shehadi et al. 1961) and recently a Japanese surgeon (Seki, 1980) has described the successful 'safe' prolongation of an upper arm tourniquet by hypothermia application. All these workers used ice and cooled the limbs for varying periods prior to tourniquet application. Little or no quantitative data were presented to establish a protective effect of hypothermia on muscles and nerves subjected to tourniquet

ischaemia. Furthermore, there appear to be practical problems associated with the application of local hypothermia as described. These include :

1. The use of water-ice bags which could create practical problems in a busy theatre.
2. The prolongation of the anaesthetic time by up to 30 minutes whilst the limb is cooled prior to tourniquet application.
3. The difficulty of cooling a well-perfused limb by 10°C, without causing marked body core cooling, must be considered. This is especially relevant in the post-operative recovery stage when marked shivering can increase a patient's oxygen requirements severalfold (Gray and Nunn 1980).

It is clear that further studies are required to determine the role of hypothermia in preventing neuromuscular damage during tourniquet-induced ischaemia.

CHAPTER FOUR

THE PROTECTIVE ROLE OF HYPOTHERMIA IN TOURNIQUET-INDUCED MUSCLE ISCHAEMIA : AN EXPERIMENTAL STUDY

4.1 INTRODUCTION

On the basis of the studies reviewed in Chapters 2 and 3, I decided to examine the protective role of hypothermia in muscles made ischaemic by the application of a tourniquet.

Landrace pigs were chosen as an experimental model because their forelimb muscles, like those of man, are of mixed type I (slow twitch) and type II (fast twitch) fibres. Other experimental animals have muscles which contain predominantly type I or type II fibres only. Thus the mixed muscles of pigs may behave in a similar fashion to those of man.

A commercially available cold gel enclosed in specially constructed plastic bags which could be wrapped closely around the limb, was used. This method of creating local hypothermia for tourniquet ischaemia has not been described before, but it appears to have the advantages of easy to apply, non-messy, re-usable and, as will be found, creates a cooling effect in the limb which lasts for at least three hours. It can also be applied to the area directly under the tourniquet where most neuromuscular damage is expected to occur. Thus, it was possible to apply the cooling immediately prior to the tourniquet application, not for half an hour prior to the procedure, as described by other authors (Paletta et al. 1961, Shehadi et al. 1961, Nakahara and Sakahasi 1967, Seki 1980).

4.2 MATERIALS AND METHODS

A. Equipment:

For producing hypothermia

A thermolabile polyglycol gel enclosed in clear plastic bags (Kay Laboratories, U.S.A.) was used to wrap around the limbs. A sealed soft rubber tube was also filled with the gel and wrapped around the limb directly under the site for the tourniquet application. These bags had previously been kept for at least 12 hours in the deep freeze, the gel remains in a soft state even when frozen.

To insulate the ice bags and to ensure they remained cold for the duration of the procedure, a sleeve of 2,5 mm thick Neoprene material (closed cell construction) was placed over the ice bags.

For Temperature Measurements

Intramuscular and skin temperatures were measured in both limbs using thermocouple probes connected to Ellab Instruments, Type TE.3 thermometers (Electrolaboratoriet, Copenhagen). The ice bag temperatures were monitored by a direct reading thermocouple connected to an oscillograph 400 MD/2 (George Washington Ltd., England). The nasal temperatures were monitored using a nasal/rectal thermometer (Yellow Springs Instrument Co. Ltd.). To prevent the skin probes monitoring the ice bag and not the skin temperature, pieces of neoprene were taped between the probes and the ice bags. All the temperature probes were calibrated and checked against each other before each experiment.

For Pressure Measurements

A LX0503A pressure transducer, measuring pressure in mmHg with a stable pressure range of up to 1520 mmHg was placed in circuit with an Intersil ICL7016 Evaluation Kit digital readout display. The components were placed in a Rose enclosure (Cat. 912208) and DC power was provided by a PPZ battery. The transducer was periodically checked and re-calibrated if necessary against a mercury manometer.

B. PROTOCOL FOR THE NORMOTHERMIC GROUP (16 Pigs)

1. Landrace pigs, 18 - 25 Kg, were anaesthetised with pentothal, intubated and ventilated with a nitrous oxide, oxygen mixture.
2. For maintenance of anaesthesia, pentothal supplementation and $N_2O:O_2$ was used. Halothane was avoided because of the risk of provoking malignant hyperthermia, to which this particular breed of pig is susceptible (Woolf et al. 1970).
3. Using sterile techniques, catheters were inserted into the carotid artery and internal jugular vein in the neck. The arterial line was used for blood pressure monitoring and blood sampling. The venous line was used for intravenous fluid maintenance during the procedure, at a rate of approximately 4.5 ml/Kg/hr.
4. For the measurement of effluent venous blood, a 16 gauge catheter was inserted into an ante cubital fossa vein of the forelimb, proximal to the tourniquet.
5. After iodine preparation of the skin, an open muscle biopsy was performed on the limb under the area where the tourniquet was

to be applied. All muscle biopsies of the ischaemic limb were taken from sites which had been under the tourniquet. The biopsy was divided into five parts of between 80 - 150 mg each, placed in Greiner tubes, stoppered and placed immediately in liquid nitrogen. The time delay from taking the biopsy to the last sample being placed in liquid nitrogen was less than 60 seconds. All biopsies were stored in liquid nitgrogen until analysed within a week for glycogen content and phosphofructokinase activity. The biopsy wounds were closed with 4,0 Ethicon sutures.

6. A 5 cm wide Kidde pneumatic tourniquet cuff was then applied to the limb and inflated to 500 mm Hg pressure for three hours. The pressure was checked using the digital read-out pressure transducer.
7. Prior to, during and after the three hours' tourniquet application, blood samples were drawn and temperatures measured (4.2 D and E).
8. After three hours the tourniquet was removed and after ten minutes another muscle biopsy taken, using the technique described in 5 (above).
9. The pig was given 1 million units' penicillin intravenously during the procedure and 200,000 units intravenously daily for four days after the procedure.
10. The pig was then monitored for a further three hours before the limb line was removed, the central line strapped in place, and the pig returned to its cage.
11. Daily for the next six days, blood samples were taken for esti-

mation of serum creatine kinase activity.

12. On the sixth day, the pig was re-anaesthetised and subjected to a further two hours' tourniquet ischaemia to the same limb. Muscle biopsies and other measurements, with the exception of temperatures and blood lactates, were taken as previously. A muscle biopsy was also taken from the corresponding muscle in the control limb.
13. Daily blood samples were taken for estimation of creatine kinase activity for a further four days. Biopsy samples were taken from the muscle of the tourniquet limb and the control limb of the anaesthetised pig just prior to administration of a pentothal overdose, on the tenth day after the initial surgery.
14. Each set of muscle biopsies was taken from the same muscle before and after the tourniquet, but from a muscle which had not been previously damaged by biopsy. Thus, with the first tourniquet, the biopsy was taken from muscle one; with the second tourniquet from muscle two and, at sacrifice, from muscle three. Muscles two and three were also biopsied on the control limb at days six and ten respectively.
15. If the pig was seen to be ill, or if the site of the indwelling catheters became infected, the pig was re-anaesthetised. Muscle biopsies were taken from the tourniquet and control limbs and the anaesthetised pig was sacrificed with an overdose of pentothal.

C. PROTOCOL FOR THE HYPOTHERMIC GROUP (11 Pigs)

1. Landrace pigs, 18 - 25 Kg were anaesthetised with pentothal and ventilated with a nitrous oxide, oxygen mixture.
2. A forelimb was prepared with iodine, a muscle biopsy taken and the tourniquet applied at 500 mmHg pressure for 3 hours.
3. Hypothermia was produced by encasing the limb, including the area under the tourniquet cuff, with bags containing the cold polyglycol gel. Hypothermia was also produced in the control limb by wrapping it with the cold gel bags.
4. To prolong the cold period, a further cover of insulating neoprene was placed over both hypothermic limbs and bags.
5. The remainder of the protocol and the measurements made were the same as for the normothermia group.

D. SYSTEMIC AND PERIPHERAL BLOOD MEASUREMENTS

Measurements of creatine kinase activity, lactate, potassium and calcium levels and pH

Blood samples for estimation of serum creatine kinase activity and lactate levels were taken from the central line prior to the tourniquet application and then at hourly intervals until the tourniquet was removed. Immediately on removal of the tourniquet, and at 5, 10, 15, 20, 30, 60, 120 and 180 minutes after tourniquet release further blood samples were taken from both the central and the peripheral lines.

Blood samples for pH, potassium and calcium levels were taken from the central line prior to and one hour after commencement of the tourniquet. Immediately on release of the tourniquet and at five minute intervals until 20 minutes had elapsed further blood samples were taken from both the central and peripheral lines.

For the next six days, blood was taken daily from the indwelling central line for estimation of creatine kinase activity. Measurements taken on day six during tourniquet re-application were similar except no limb lines were inserted. Blood was drawn from the central line prior to the general anaesthetic, during the two hour tourniquet time, and at 5, 10, 15, 20, 30 60 and 180 minutes after tourniquet release.

For the next four days, daily blood samples were drawn daily from the indwelling central line for estimation of creatine kinase activity.

E. SKIN, MUSCLE AND NASAL TEMPERATURE MEASUREMENTS

The nasal, intramuscular and skin temperatures of both the tourniquet and the control limbs were recorded every five minutes from immediately before, and for 30 minutes after tourniquet application. Thereafter temperatures were recorded at 45, 60, 90, 120, 150 and 180 minutes.

On release of the tourniquet, the temperatures were recorded every two minutes for 10 minutes, then every 5 minutes until 30 mintes and, thereafter at 45, 60, 90, 120, 150 and 180 minutes.

4.3 STATISTICAL METHODS USED

The raw data were analysed, using two-way and three-way Analysis of Variance (ANOVA) techniques. Acceptance intervals of the mean were used to determine significance at $p < 0,05$ levels.

4.4. EXPERIMENTAL RESULTS

A. During the Tourniquet Application

Metabolic and biochemical parameters

There were no significant differences in serum creatine kinase activity, pH, potassium, or sodium levels between the hypothermic and normothermic groups during the three hours of tourniquet application. (Table 4.1)

TABLE 4:1 METABOLIC AND BIOCHEMICAL PARAMETERS DURING THE TOURNIQUET

Parameter measured during tourniquet application	HYPOTHERMIC GROUP n=10		NORMOTHERMIC GROUP n=11	
	Mean	S.D.	Mean	S.D.
Creatine kinase (CK) IU/L	160,00	110,80	310,00	225,00
Lactate (central) mole/m	0,94	0,33	1,41	0,65
Hydrogen Ion concentration (pH)	7,52	0,08	7,57	0,07
Potassium (K+) mmole/L	3,95	0,46	3,70	0,19
Sodium (Na+) mmole/L	131,20	2,80	136,70	3,60

Values expressed as means $\pm$ S.D. There were no significant differences between any values in the two groups.

Central, Muscle and Skin Temperatures

Apart from the first central (nasal) temperature prior to tourniquet application, there was no significant difference between the central (nasal) temperature of the hypothermic and normothermic groups. (Table 4.2)

TABLE 4.2 CENTRAL TEMPERATURES (°C) DURING TOURNIQUET APPLICATION

Duration of tourniquet application (minutes)	NORMOTHERMIC GROUP n = 11		HYPOTHERMIC GROUP n = 10	
PRE	37,0	0,52	38,0	1 *
5	37,4	0,58	38,2	0,91
10	37,5	0,62	38,3	0,80
15	37,5	0,67	38,2	0,85
20	37,5	0,65	38,2	0,88
25	37,5	0,64	38,1	0,90
30	37,5	0,65	38,2	0,88
35	37,6	0,69	38,0	0,86
40	37,6	0,71	38,0	0,86
45	37,7	0,75	37,9	0,87
60	37,9	0,92	37,9	0,95
90	38,4	1.04	37,9	0,84
120	38,6	1,07	37,9	0,81
150	38,8	1,13	38,0	0,97
180	38,6	1,02	38,2	0,99

* $p < 0,05$

Values expressed as means $\pm$ S.D.

The muscle temperature of the ischaemic limb of the normothermic group fell progressively until about 90 minutes after tourniquet application, at which time it levelled off (Figure 1). The control limb muscle temperature of the normothermic group rose gradually during the tourniquet application following the similar gradual rise in the central temperature. (Table 4.2)

The muscle temperature of the ischaemic limb of the hypothermic group showed a rapid fall to very low levels (±16°C) over the first 45 - 60 minutes and then levelled off for a further 30 minutes. Thereafter it rose gradually (Figure 2). After three hours' tourniquet application the muscle temperature remained significantly lower ($p < 0,0001$) than the ischaemic limb of the normothermic group. The temperature of the hypothermic control limb muscle fell almost as rapidly as that of the ischaemic limb, reaching a minimum at about 40 minutes. Thereafter, the muscle temperature rose, although after three hours it was still significantly ($p < 0,01$) lower than its temperature had been prior to cooling.

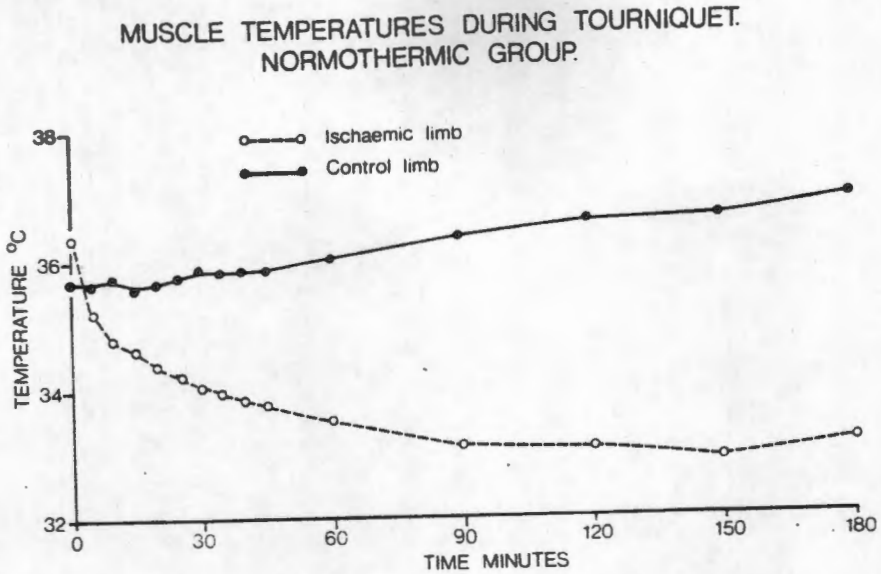


FIGURE 1 NORMOTHERMIC GROUP

Note the progressive fall in muscle temperature of the ischaemic limb for 90 minutes. The control limb muscle temperature rises gradually during the three hours of tourniquet application.
Results expressed as mean for 11 experiments, with no S.D. difference between the two.

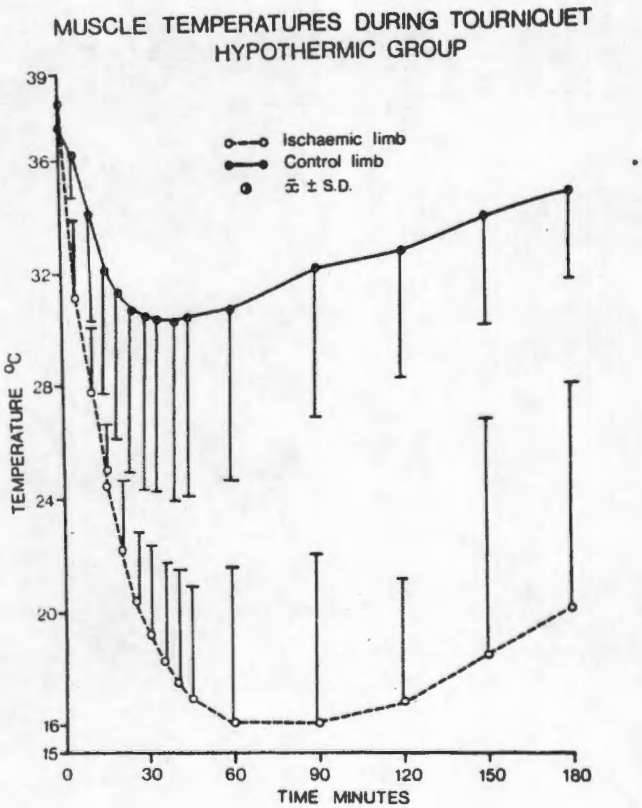


FIGURE 2 HYPOTHERMIC GROUP

Note the rapid fall in muscle temperature of both the ischaemic and control limbs and the subsequent gradual rise.
Results expressed as mean for 10 experiments.

The skin temperature of the ischaemic limb of the normothermic group fell steadily during the three hours' tourniquet application. The skin temperature of the control limb of the normothermic group rose gradually following the slow rise in the nasal and muscle temperatures. (Figure 3)

The skin temperature of the ischaemic limb of the hypothermic group fell rapidly during the first two hours' tourniquet, reaching a minimum temperature of ± 9°C. The temperature then rose 3°C during the final hour of tourniquet application. The skin temperature of the control limb of the hypothermic group also fell, reaching a minimum value of ± 26°C after about 40 minutes and thereafter gradually rising. At the end of the experiment, the skin of the control limb in the hypothermic group was still significantly cooler ($p < 0,01$) than at the start of the experiment (Figure 4).

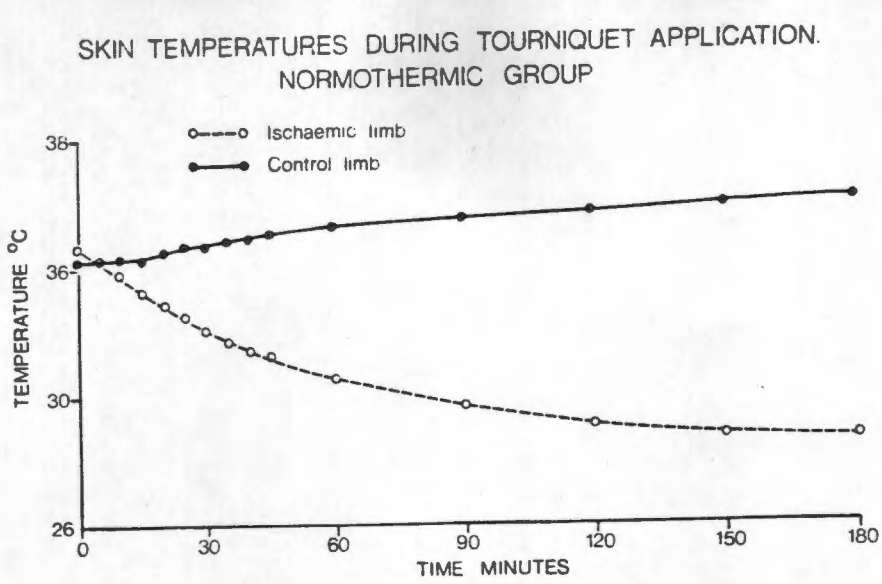


FIGURE 3 NORMOTHERMIC GROUP

Note the progressive fall in skin temperature of the ischaemic limb and the slow rise in skin temperature of the control limb.
Results expressed as mean for 11 experiments, with no S.D. difference between the two.

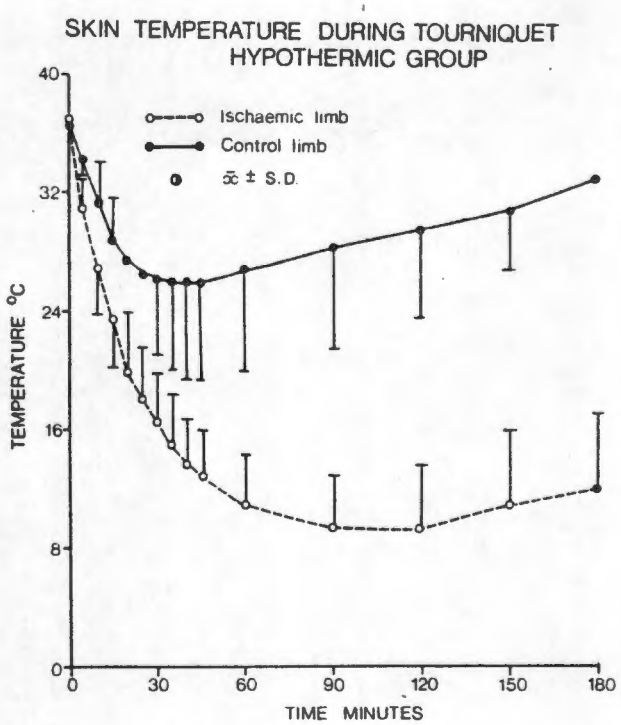


FIGURE 4 HYPOTHERMIC GROUP

Note the rapid fall in skin temperatures of both the ischaemic and control limbs and the subsequent gradual rise.
Results expressed as mean for 10 experiments.

B. AFTER TOURNIQUET RELEASE

Serum Lactate Levels (μmole/ml)

Values measured in the carotid artery : central levels

There was no significant difference in serum lactate levels between the hypothermic and normothermic groups until two hours after tourniquet release. The lactate levels in the normothermic group then rose significantly above the levels in the hypothermic group (Figure 5).

Values measured in the ante cubital vein of the tourniquet limb : peripheral levels

Peripheral lactate levels were significantly higher in the normothermic group for the first 15 minutes, and again between two and three hours after tourniquet release. (Figure 6)

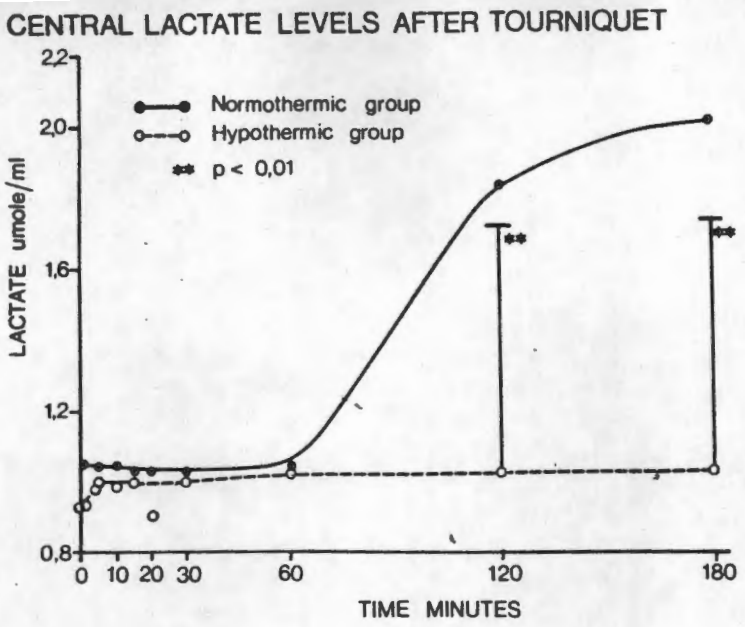


FIGURE 5 CENTRAL LACTATE LEVELS MEASURED IN A CAROTID ARTERY

Note the significant elevation of the carotid artery lactate levels in the normothermic group 120 and 180 minutes after tourniquet release.
Results expressed as mean for 10 experiments in each group with acceptance intervals of the mean at 120 and 180 minutes.

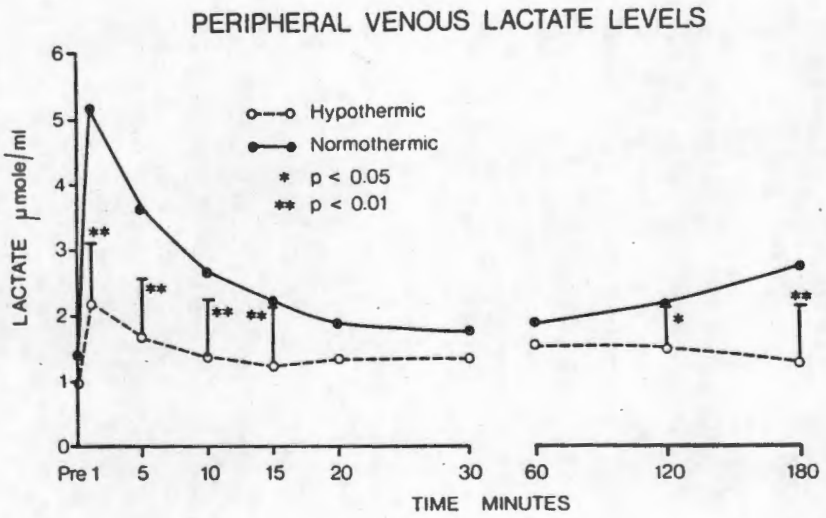


FIGURE 6 PERIPHERAL LACTATE LEVELS MEASURED IN AN ANTECUBITAL VEIN

Note the significant elevation of venous lactate levels in the normothermic group for 15 minutes after tourniquet release, and again at 120 and 180 minutes.
Results expressed as mean for 10 experiments in each group with acceptance intervals of the mean at 1, 5, 10, 15, 120 and 180 minutes.

Blood pH

The venous blood pH was significantly higher in the hypothermic group on release of the tourniquet and had returned to baseline levels within five minutes of tourniquet release. In contrast, pH of the normothermic group had not returned to baseline levels even 15 minutes after tourniquet release (Figure 7).

The arterial pH measured in the carotid artery remained stable during the tourniquet application and did not alter with its release. (Data not shown)

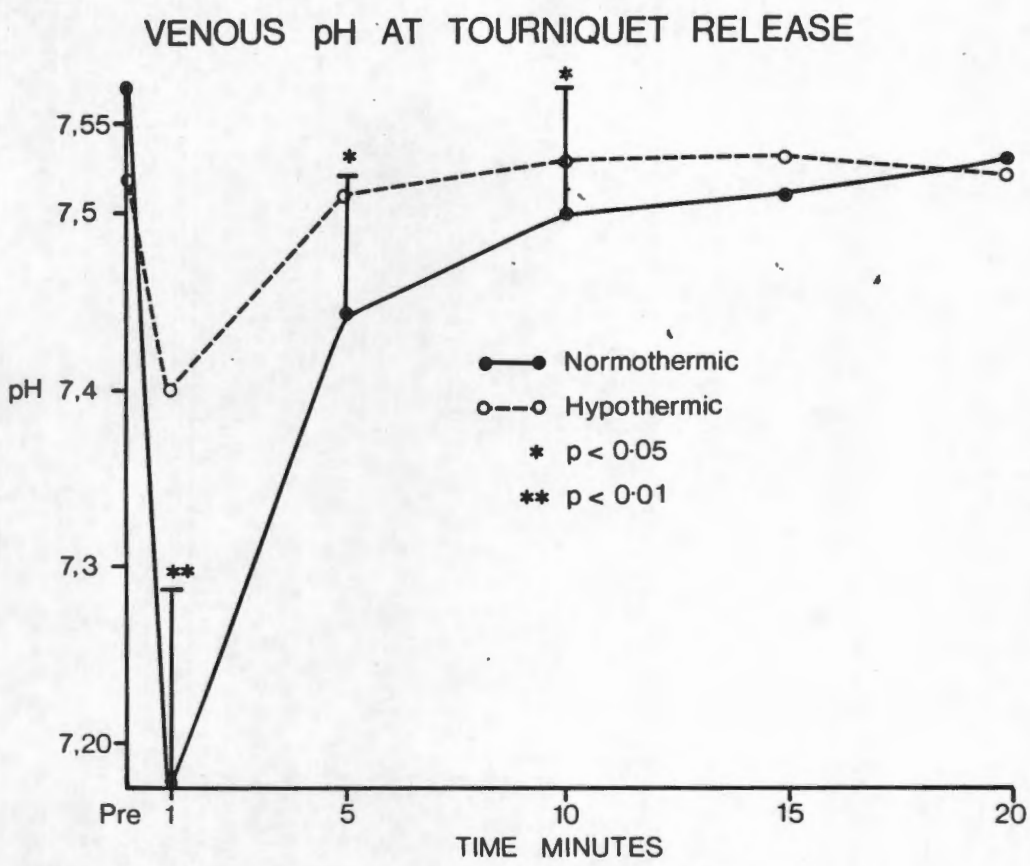


FIGURE 7
Note the significantly lower venous pH in the normothermic group and the slow return to baseline.
Results expressed as mean for 8 experiments in each group with acceptance intervals of the mean to baseline values at 1, 5 and 10 minutes.

Serum Potassium Levels (mmole/litre) - Measured in the peripheral vein of the ischaemic limb

On release of the tourniquet there was a significant rise in serum potassium levels in the effluent venous blood of both the hypothermic and normothermic groups. However, potassium levels of the hypothermic group returned to baseline levels within 10 minutes, whereas the potassium levels of the normothermic group were still significantly raised 20 minutes after tourniquet release. (Figure 8)

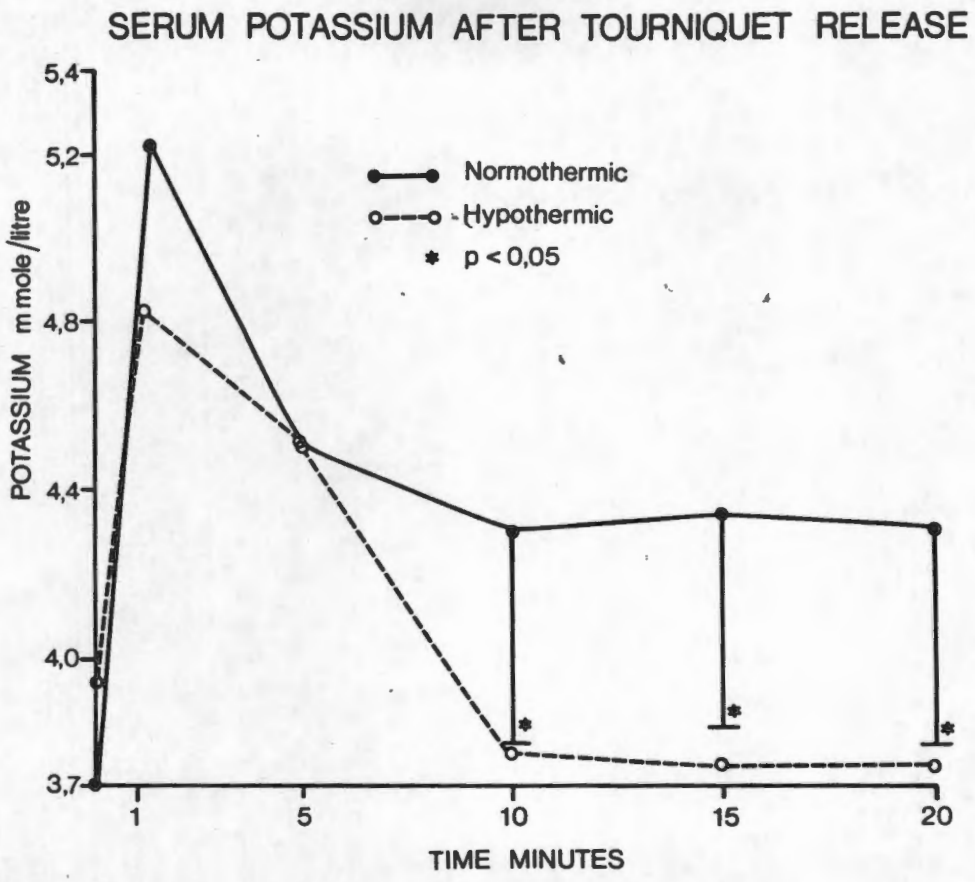


FIGURE 8

Note the significant elevation of the serum potassium of the normothermic group and its continued elevation above baseline levels, even 20 minutes after tourniquet release.
Results expressed as mean for 9 experiments in each group.
Acceptance intervals of the mean are included at 10, 15 and 20 minutes.

Serum Calcium Levels (mmole/litre)

There were no significant differences in serum calcium levels between the hypothermic and normothermic groups, nor was there any significant change with time. (Table 4.3)

Serum Sodium Levels (mmole/litre)

There were no significant differences in serum sodium levels between the hypothermic and normothermic groups. (Table 4.3)

TABLE 4.3 SERUM SODIUM AND CALCIUM LEVELS (mmole/litre)

Time after tourniquet release (minutes)	HYPOTHERMIC GROUP n = 10				NORMOTHERMIC GROUP n = 11			
	sodium		calcium		sodium		calcium	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PRE	131	2,8	2,4	0,24	137	3,6	2,5	0,17
0,1	129	2,9	2,3	0,42	138	4,8	2,3	0,25
5	129	2,1	2,2	0,32	133	7,9	2,2	0,28
10	128	2,6	2,2	0,22	134	6,7	2,3	0,32
15	128	2,8	2,2	0,36	134	7,1	2,2	0,24
20	128	3,1	2,2	0,51	133	7,0	2,2	0,16

Results are expressed as means ± S.D.
No significant differences were found

Serum Creatine Kinase (CK) activity (IU/litre)

After release of the intial tourniquet there were no significant differences in serum CK activity between the two groups, although the range of values was very large. The CK activity rose with time for both groups, reaching maximum values three hours after tourniquet release (Figure 9). Thereafter, there was a linear fall in CK activity in both groups, reaching low levels about day 5 (Figure 10).

Some specimens of serum were analysed for CK isoenzyme activities after the first tourniquet. All three CK isoenzymes, MB, BB and MM were found in the serum after the first tourniquet application. (Data not shown)

After removal of the second tourniquet on day six, there was again a rapid linear rise in serum CK activity. The rise was again maximum at three hours, but was significantly less than the rise after release of the first tourniquet. The ranges in CK activity were again very large and no significant differences were found between the normothermic and hypothermic groups (Figure 11). Serum CK isoenzyme activities were not measured after the second tourniquet.

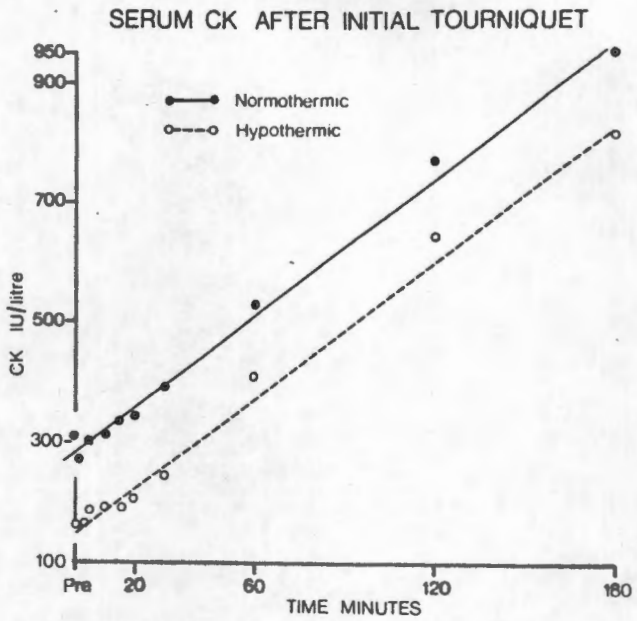


FIGURE 9

Note the rapid rise of serum CK activity of both groups after tourniquet release. Results expressed as mean for 10 experiments in each group.

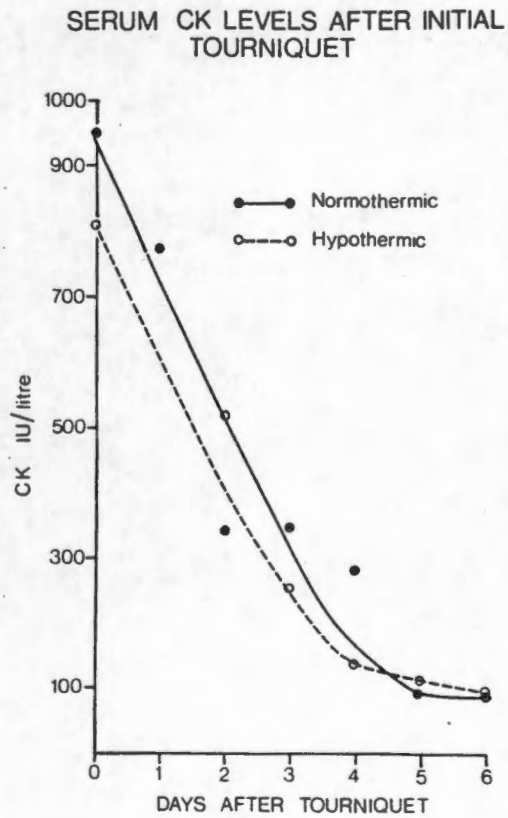


FIGURE 10

Note the rapid fall in serum CK activity during the six days after tourniquet release.
Results expressed as mean for 7 experiments in the hypothermic and 8 in the normothermic group.

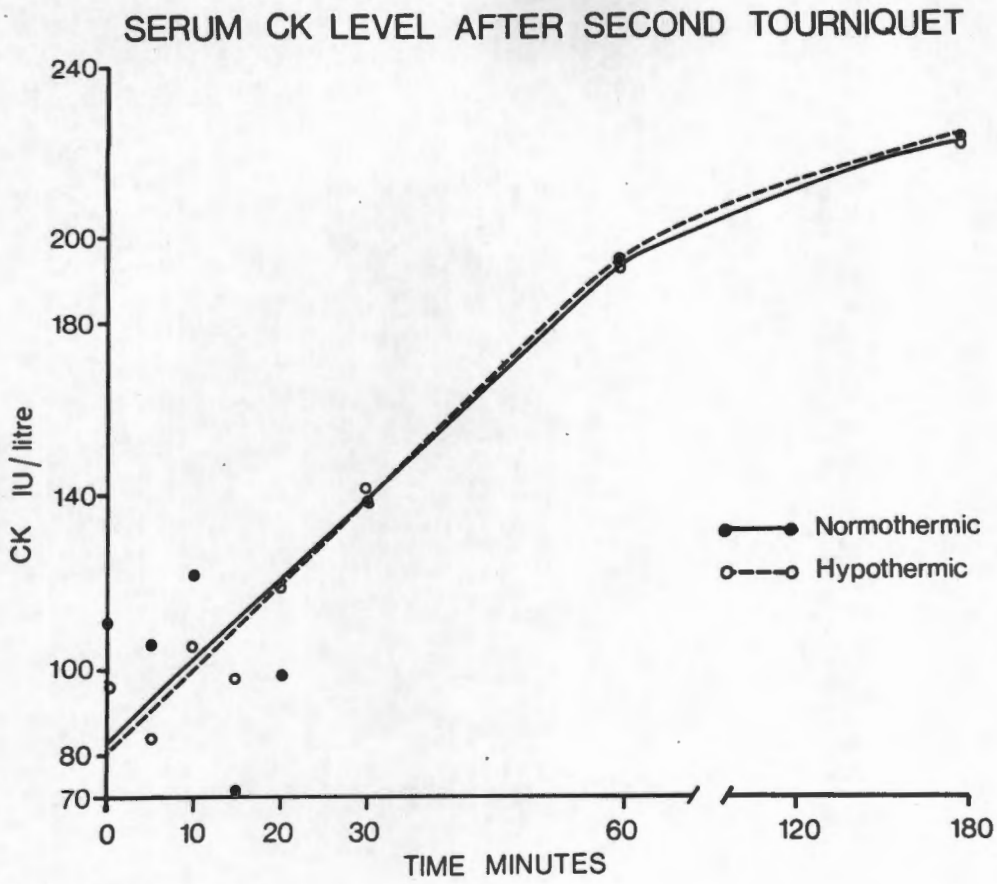


FIGURE 11

Note the rapid rise in CK activity after release of the second tourniquet and that peak levels are lower than after the first tourniquet.
Results expressed as mean for 7 experiments in the hypothermic and 8 in the normothermic group.

Muscle phosphofructokinase activity, mole/min/g wet wt

There was no significant difference in phosphofructokinase (PFK) activity either before or after either of the two tourniquet applications or between groups. (Figure 12)

At sacrifice, four days after the second tourniquet, PFK activity in the ischaemic limb of the normothermic group was significantly lower than the PFK activity in the muscle of its control limb. There was no significant difference between the PFK activity in the control and the ischaemic limb of the hypothermic group. (Figure 13)

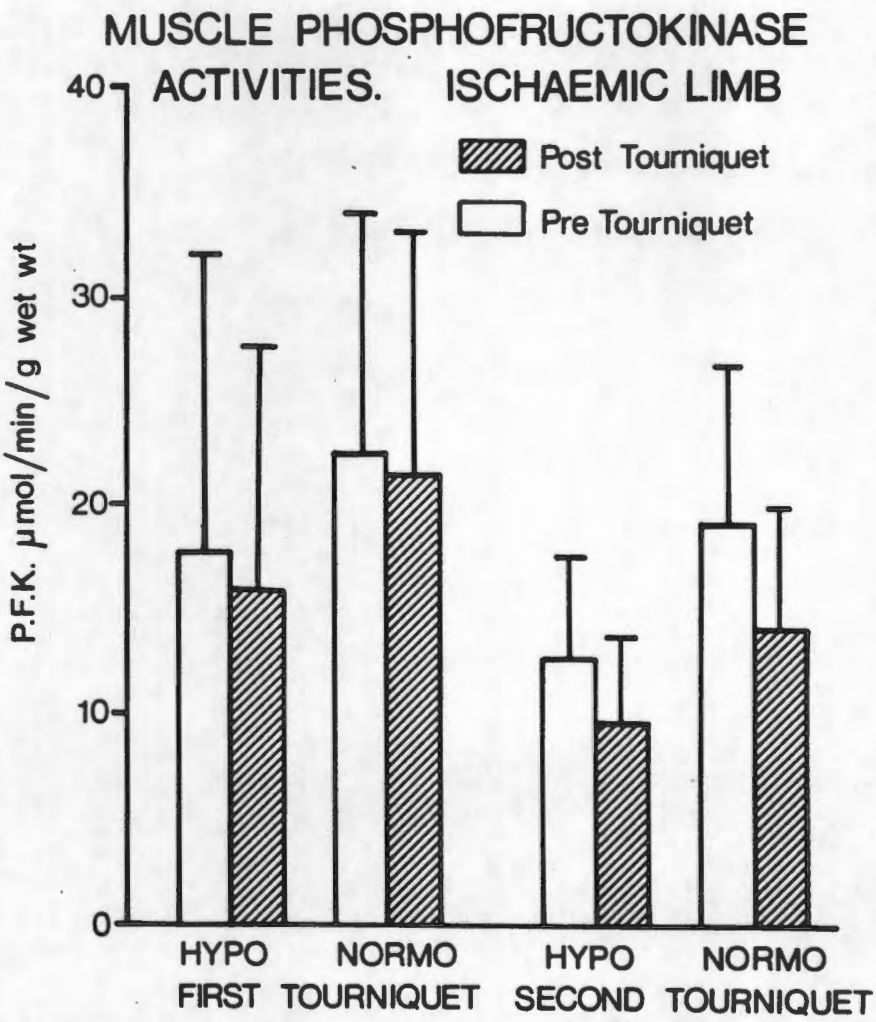


FIGURE 12

Note there is no significant difference between the two groups before and after either tourniquet application. Results are expressed as mean ± S.D. for 10 experiments in both groups.

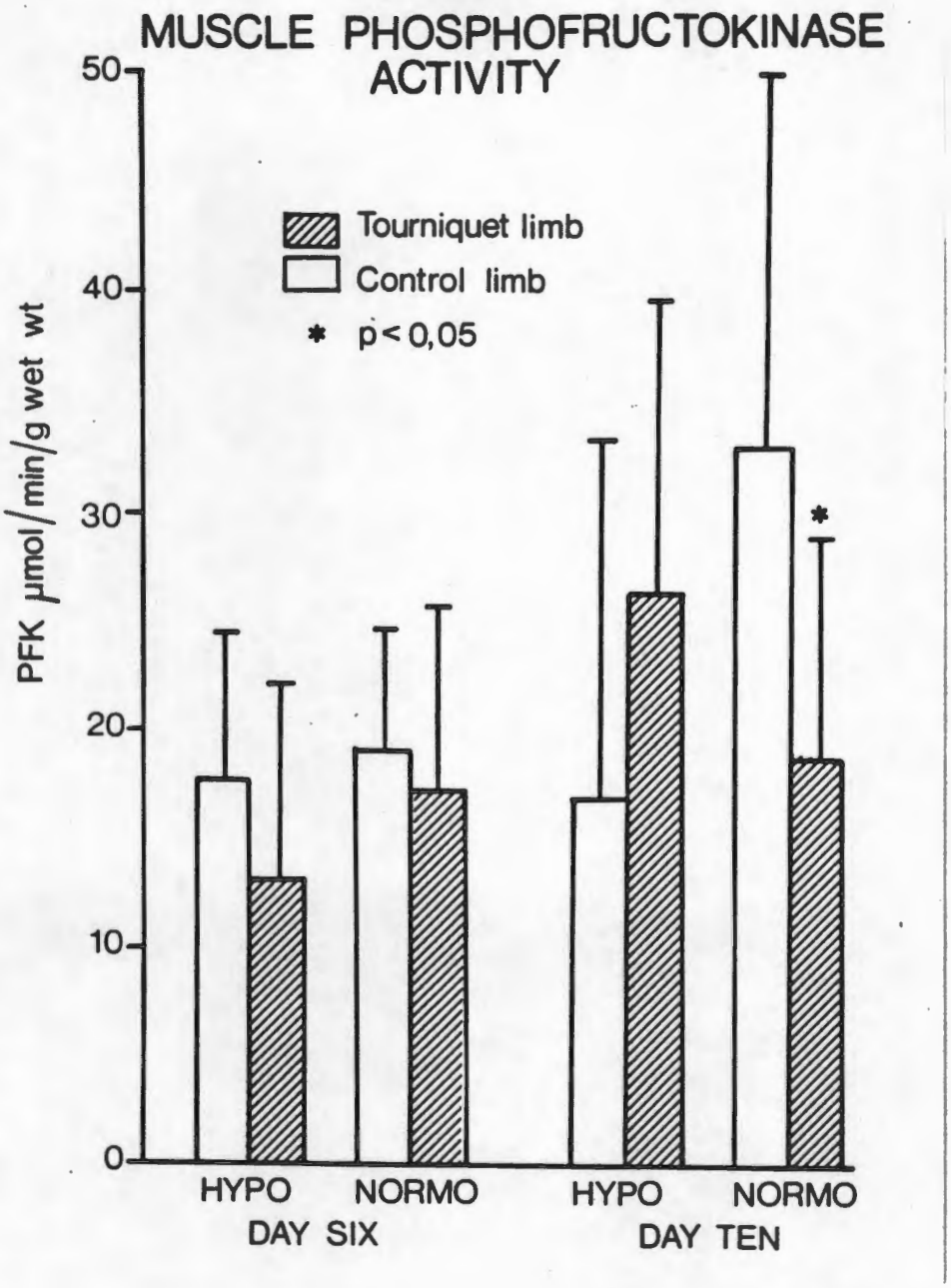


FIGURE 13

Note that there is no significant difference in PFK activity between the groups on day six. On day ten, the PFK activity is significantly lower in the ischaemic muscle of the normothermic group when compared to its control limb. Results expressed as mean ± S.D. PFK activity for 9 experiments in both groups.

Muscle Glycogen content (mmole glucose equivalents/Kg wet muscle wt)

The glycogen content of the control muscles of the normothermic group was significantly higher at the start of the experiment, and on days six and ten when compared to the control limb of the hypothermic group. This indicates two different pig populations, the group which had been randomly selected for the normothermic group appearing to have a greater glycogen storage capacity than those in the hypothermic group.

There was a highly significant fall in glycogen content of the ischaemic muscle during the first tourniquet application in the normothermic group. No such fall occurred in the ischaemic muscle of the hypothermic group. During the second tourniquet application, under normothermic conditions, there was a significant fall in glycogen content in the group previously subjected to hypothermia, but not in the normothermic group (Figure 14).

Muscle glycogen content of the ischaemic limb of the normothermic group was significantly lower on day 6 than its control, whereas no such difference was found in the hypothermic group. At day ten the ischaemic limb of the hypothermic group had a significantly elevated muscle glycogen content. Muscle glycogen content of the control limbs of both groups and of the ischaemic limb of the hypothermic group rose as the experiment progressed (Figure 15).

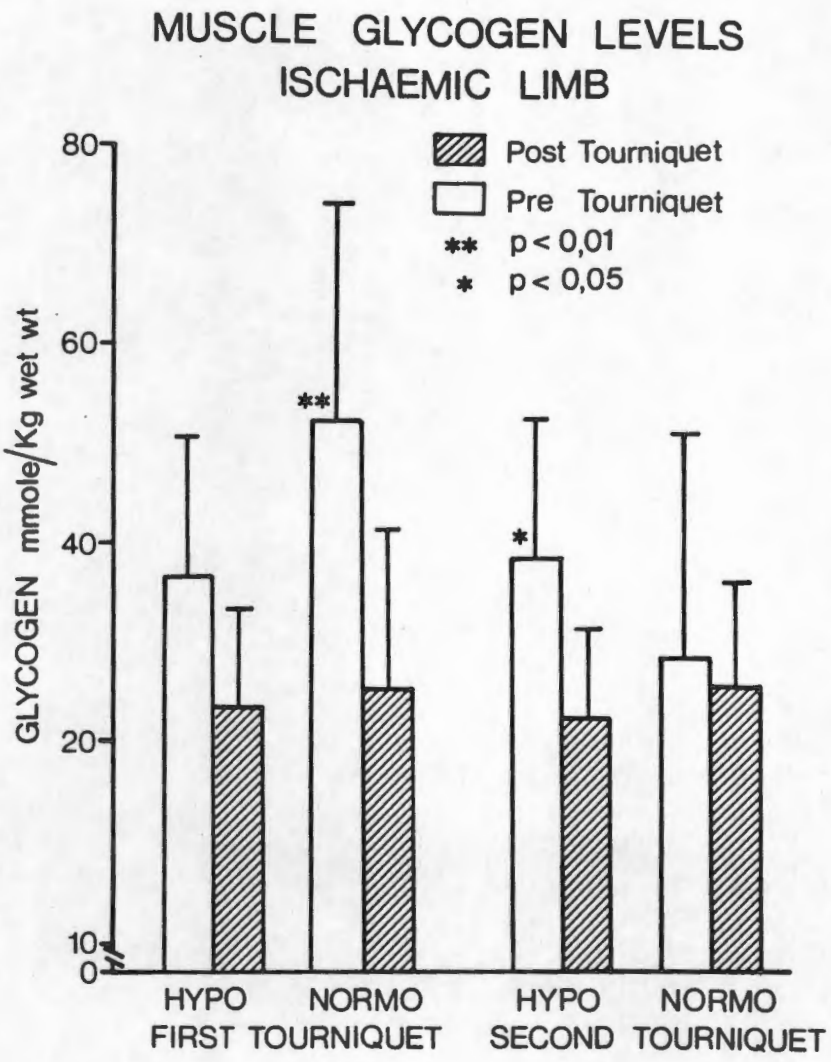


FIGURE 14

Note the significant fall in muscle glycogen content before and after the first tourniquet in the normothermic but not in the hypothermic group. Note also the fall in muscle glycogen content of the previously hypothermic limb but not in the normothermic limb during the second tourniquet application in which cooling was not employed.
Glycogen results are expressed as mean + S.D. (mmole glucose equivalents/Kg wet muscle weight) for $\overline{10}$ experiments in the hypothermic and 11 experiments in the normothermic group.

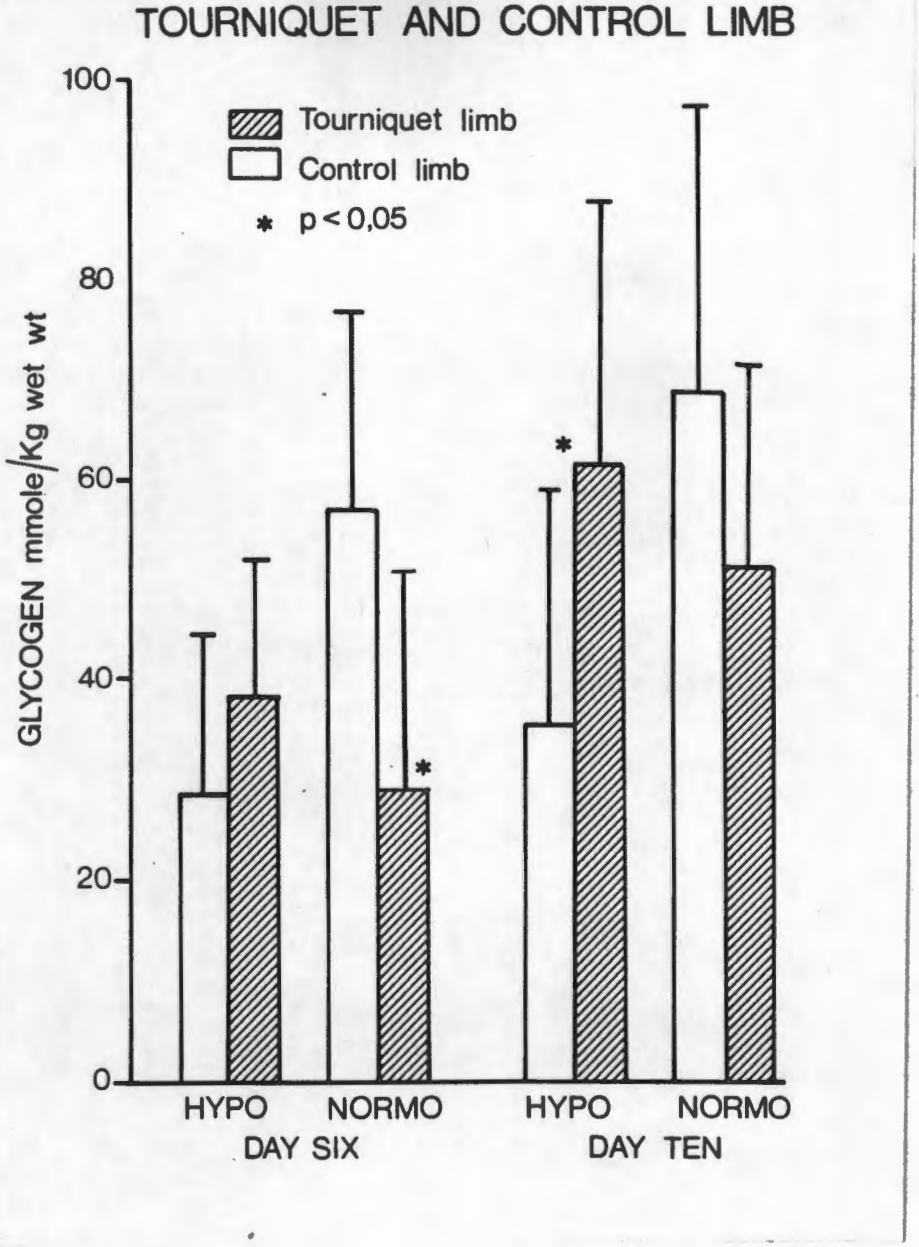


FIGURE 15

Note the different muscle glycogen levels in the two groups. The normothermic group has higher muscle glycogen content than the hypothermic group in the control limb on both day six and day ten. At day six, the glycogen content of the ischaemic muscle in the normothermic group is significantly lower than its control. On day ten, muscle glycogen content in the hypothermic ischaemic limb is significantly higher than its control.
Glycogen results are expressed as mean $\pm$ S.D. in (mmole glucose equivalent/Kg wet muscle weight) for 9 experiments in both groups.

Sudden death and muscle glycogen content

During the course of the experiment, six pigs died suddenly within four days of the first tourniquet application. Of these six pigs, five were in the normothermic group and one in the hypothermic group.

On analysis of the muscle biopsies, it was found that four of the normothermic and the one hypothermic pig had muscle glycogen levels less than 3 mmole glucose equivalents/Kg wet wt., after release of the tourniquet. Prior to tourniquet application, their muscle glycogen levels had been within the normal range.

The other parameters measured temperature of lactate, pH, potassium and creatinine kinase during and after the first tourniquet. All fell within the experimental range. All results of this sub-group were removed from the data analysed and presented.

Temperatures °C

Central (Nasal) Temperature °C

There was no significant difference in nasal temperatures between the normothermic and hypothermic groups on release of the tourniquet (Table 4.4.).

TABLE 4.4 CENTRAL TEMPERATURES (°C)

Time after tourniquet Release (Minutes)	NORMOTHERMIC GROUP n = 11		HYPOTHERMIC GROUP n = 10	
0	38,7	1,14	38,38	1,0
2	38.6	1,14	38,33	1,05
4	38,5	1.20	38,13	0,90
6	38,5	1,23	38,1	0,90
8	38,5	1,20	38,08	0,90
10	38,5	1,21	38,11	0,92
15	38,5	1,22	38,05	0,96
20	38,5	1,25	38,11	0,96
25	38,5	1,25	38,16	0,99
30	38,6	1,26	38,25	0,88
45	38,6	1,32	38,26	0,90
60	38,5	1,32	38,21	0,90
75	38,9	0,81	38,38	0,80
90	38,9	0,80	38,51	0,86
120	38,5	0,89	36,61	1,00
180	38,4	1,47	38,68	1,47
Values are expressed as	Means ± S.D.			

Muscle Temperatures °C

The muscle temperature of the ischaemic limb of both groups returned to control values within four minutes of tourniquet release. Thereafter the muscle temperature of the ischaemic limb of both groups became higher than that of the control limb. In the normothermic group, this rise became significant between 30

and 90 minutes post-tourniquet release and was still higher, although not significantly, at 3 hours (Figure 16). In contrast, the muscle temperature of the hypothermic group's ischaemic limb was never significantly above control values. (Figure 17)

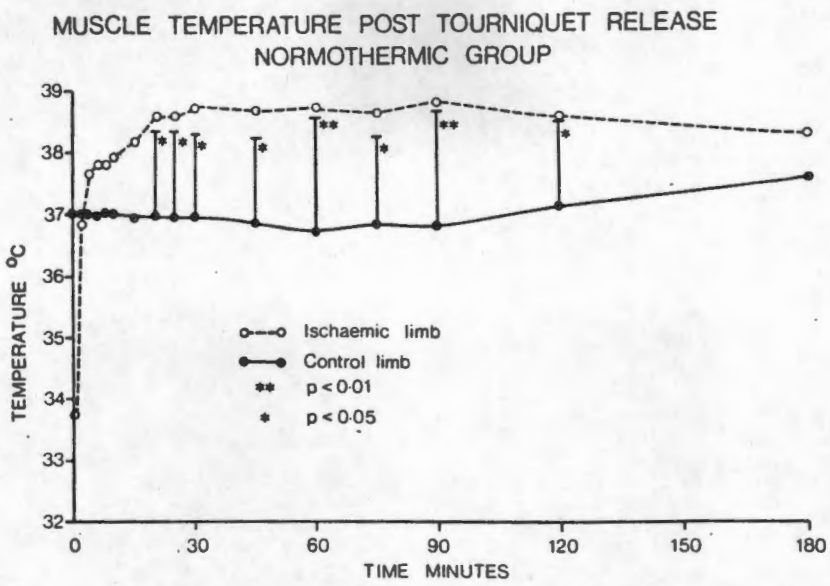


FIGURE 16 NORMOTHERMIC GROUP

Note the significant elevation of the muscle temperature of the ischaemic limb above that of the control limb from 30 to 120 minutes after tourniquet release.
Results expressed as mean for 11 experiments. Acceptance intervals of the mean are shown between 30 and 120 minutes.

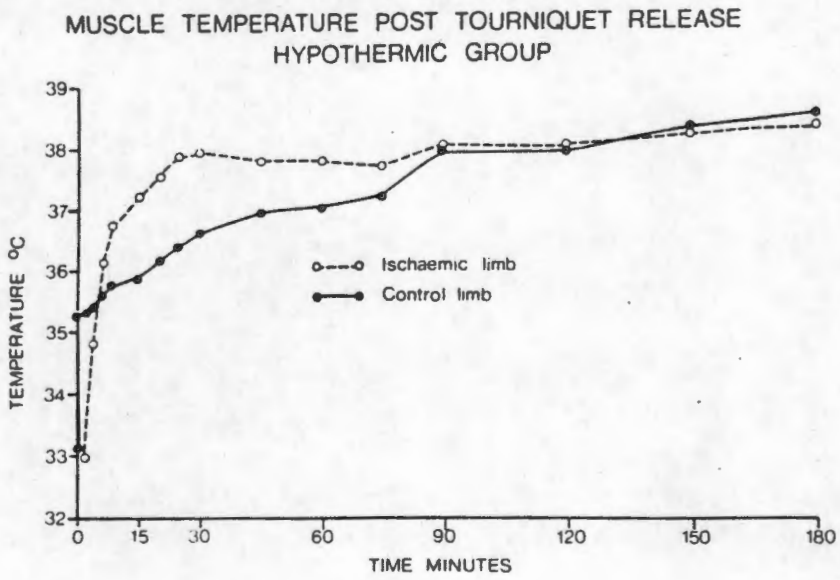


FIGURE 17 HYPOTHERMIC GROUP

Note that there is no significant difference in muscle temperature between the ischaemic and control limbs after tourniquet release.
Results expressed as mean for 10 experiments.

Skin Temperatures °C

The skin temperatures of both the ischaemic hypothermic and ischaemic normothermic limbs returned to control levels within four minutes of tourniquet release. In the ischaemic limb of the normothermic group there was an overshoot in skin temperature, above that of the control limb, which reached significant levels between 45 and 90 minutes after tourniquet release (Figure 18). The skin temperature of the ischaemic limb of the hypothermic group also increased above that of the control limb for a short period after tourniquet release, but this increase was not significant (Figure 19).

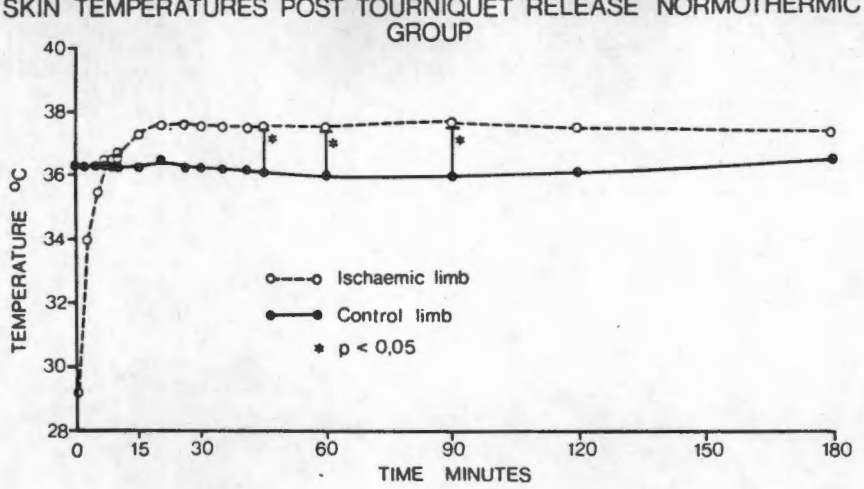


FIGURE 18 NORMOTHERMIC GROUP

Note the significant elevation of the skin temperature of the ischaemic limb from 45 to 90 minutes after tourniquet release.
Results expressed as mean for 11 experiments with acceptance intervals of the mean at 45, 60 and 90 minutes.

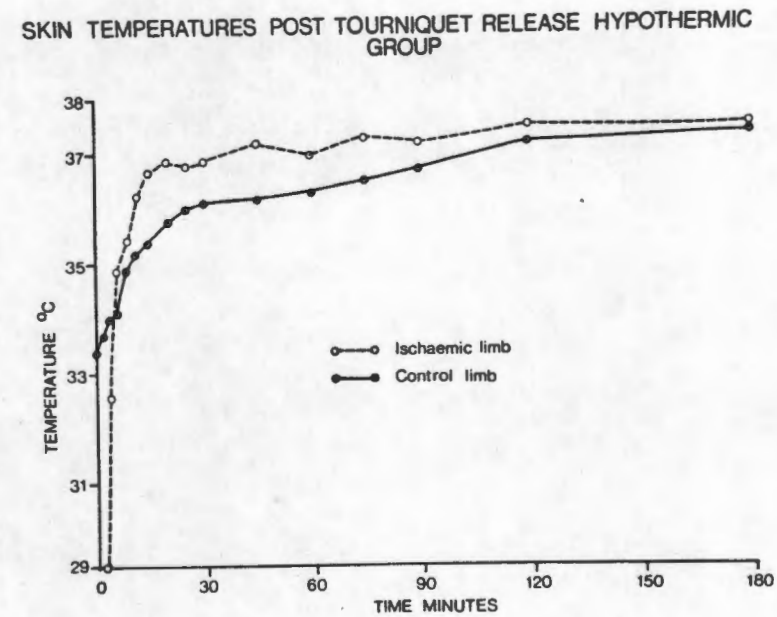


FIGURE 19 HYPOTHERMIC GROUP

Note that there is no significant difference in skin temperature between the ischaemic and control limbs after tourniquet release.
Results expressed as mean for 10 experiments.

4.5 DISCUSSION OF THE RESULTS

A. Principal Findings

The principal findings of this study are that this method of hypothermia application is both effective and safe and that hypothermia provides some protection to muscles exposed to tourniquet induced ischaemia. Evidence for the protective role of hypothermia is the slowing of glycogenolysis and hydrogen ion production during ischaemia, reduced potassium efflux from muscle and minimal inflammatory response on release of the tourniquet, a faster rate of biochemical and metabolic recovery, and reduced muscle cell damage.

B. Safety and efficacy of this method of hypothermia

The use of cold gel packs on the limb was found to be convenient and safe. Skin temperatures as low as 5°C (mean 9,3°C) and muscle temperatures as low as 11°C (mean 16°C) were produced by close application of the cold packs insulated in a neoprene sleeve. No cases of ice burns, as evidenced by severe erythema or blistering, were seen in any of the ten animals who were subjected to hypothermia.

During the days following the first tourniquet, the pigs who had undergone local limb hypothermia appeared to be in better general condition and to limp less when compared to the normothermic group. Similar findings were reported in limbs of dogs who had been subjected to tourniquet application under hypothermia (Paletta et al. 1961) and were considered to be due to decreased oedema formation in the ischaemic limb.

During the period of tourniquet application, no significant differences were found between the hypothermic and normothermic groups in serum creatine kinase activity, serum lactate, serum potassium, serum sodium and sodium calcium levels, nor in pH or nasal temperatures. This implies that the ischaemic limb is effectively isolated from the rest of the body by the tourniquet, as was also reported by Klenerman et al. (1980). Thus, the changes measured are due to local hypothermia and not to whole body cooling.

C. Beneficial effects of hypothermia

I. Local muscle metabolism

Hypothermia produced a significant slowing in tissue metabolism as shown by the smaller fall in blood pH (Figure 7) and muscle glycogen content (Figure 14) during ischaemia, and the smaller rise in serum lactate levels (Figure 6) in the hypothermic limbs on tourniquet release. This slowing of metabolism is believed to have a protective role in ischaemia (Seki 1980, Haljamäë 1970, Hagberg et al. 1970).

II. Muscle and skin temperatures

The rapid return of skin temperature to control levels after tourniquet release is well documented (Sanders 1973, Modig et al. 1978, Déry et al. 1965, Harris et al. 1975). The elevation of the skin temperature of the ischaemic limb above control values has also been reported by some, but not all, workers (Modig et al. 1978, Sanders 1973). The finding in this study that the temperature of

the recently ischaemic muscle and skin of the normothermic group, but not of the hypothermic group, rises above that of the control limb, indicates the possibnility of acontinued inflammatory reaction. This supports the hypothesis that fewer breakdown products of ischaemia causing an inflammatory reaction are produced in the hypothermic muscle and skin.

III. Local muscle damage

The high tourniquet pressure (500 mmHg) applied to the relatively small muscle mass of the pig's forelimb, for three and then two hours, caused significant damage to the muscle. This was shown by the large rise in serum creatine kinase activity after release of the first and second tourniquets in both the hypothermic and normothermic groups. Unfortunately, whilst serum CK activity has been used as an accurate index of muscle damage in dogs (Chiu et al. 1976, Heppenstall et al. 1979) and in humans (Santavirta et al. 1978), it is a poor marker in South African Landrace pigs. Mitchell and Heffron (1975) reported that the serum CK activity in this breed of pig varies considerably with age, time of blood sampling and especially the stress to which the animal is exposed at the time of sampling. Thus, in the present experiments, the ranges of serum CK activity taken from the pigs prior to tourniquet application were extremely large (80 - 800 IU/litre) and this may have obscured any beneficial effect of hypothermia.

As intracellular potassium levels (140 mmole/L) are much greater than serum levels (2,5 - 4,0 mmole/L), damage to tissue membranes causes potassium efflux, thereby raising serum potassium levels. Therefore, the higher serum potassium levels in the normothermic group even 20 minutes after tourniquet release indicates more severe muscle damage than occurred in the hypothermic group (Figure 8). Continuing elevated potassium levels after tourniquet release have been reported by other authors (Klenerman 1980, Modig et al. 1978, Jennische et al. 1982) and may indicate continuing muscle ischaemia.

Muscle glycogen content, and the activity of the glycogen rate limiting enzyme phosphofructokinase, were used as indicators of the viability of the limb muscles. There were no significant differences in PFK activity before and after the two tourniquet applications, nor between the control and ischaemic limbs of both the hypothermic and normothermic groups at day six (Figures 12 and 13). However, the assay used only assesses the quantity of enzyme present and not its in vivo functioning. Levels of PFK activity found were similar to that found in other mammals (E.A. Newsholme, Personal communication). At day ten, muscle PFK activity in the ischaemic limb of the normothermic group was significantly lower than the control limb, possibly indicating damaged muscle tissue and destruction of the enzyme in the ischaemic limb. By contrast, at day ten, there was no difference in the PFK activity of the ischaemic and control limbs of the hypothermic group. Similarly, at day ten, the glycogen levels in the ischaemic limb muscle of the

normothermic group were lower than those of the control limb, further indicating damaged muscle tissue in the ischaemic limb. However, the fact that the muscle of the ischaemic limb of the hypothermic group had significantly higher stores than their control limbs (Figure 15), indicates that the muscle cells of the ischaemic limb of the hypothermic group were functioning normally, at least with regard to glycogen storage capacity.

Thus, by subjecting the pig's forelimb to a second tourniquet, the muscle cells which were only marginally viable after the first tourniquet were further damaged. That the hypothermic group's muscle cells had been at least partially protected during the initial tourniquet was shown by the normal muscle PFK activities and glycogen content four days after the second tourniquet. The muscle cells of the normothermic group in contrast showed evidence of impaired biochemical function.

The general elevation in glycogen content in the control limbs of both groups and the ischaemic limb of the hypothermic group is probably due to the fact that during the experiment the pigs were in individual cages and on an ad libitum diet. Prior to the experiment they had had to fight for their food in communal pens.

IV. Rate of recovery

The ischaemic limbs of both the hypothermic and normothermic group developed reactive hyperaemia upon release of the tourniquet. This was shown by flushing of the skin, a rapid rise in skin and muscle

temperature and the maximum rise in serum potassium levels within the first minute after tourniquet release. The maximum elevation in potassium levels in the venous blood draining the limb on tourniquet removal, has been shown to correspond with maximum blood flow into the limb (Jennische et al. 1982).

The hypothermic group had a significantly faster return to pre-tourniquet levels of serum lactate, potassium and pH after the initial tourniquet. This indicates both a lesser degree of tissue damage and a more rapid rate of recovery.

5. Premature Deaths

The cause of the sudden deaths in five pigs (four normothermic and 1 hypothermic) within three to four days of the first tourniquet application, is unknown. The only remarkable feature common to all was a marked fall in muscle glycogen after tourniquet removal (to 3 mmole/Kg wet wt). None of the surviving pigs showed this substantial drop in glycogen content. One animal, also in the normothermic group, died from septicaemic shock after the second tourniquet application, despite prophylactic penicillin. This animal had been sick prior to the second anaesthesia but this had gone unnoticed.

It is interesting to note that, of the six early deaths, five were in the normothermic group. The data of all six animals were removed from the final analysis of the results and thus, of the original 27 animals, only 21 have been included in the present study.

4.6 SUMMARY AND CONCLUSION OF THE EXPERIMENTS TO STUDY THE EFFECT OF LOCAL HYPOTHERMIA IN TOURNIQUET INDUCED MUSCLE ISCHAEMIA

The application of cold gel packs was found to be safe and effective in reducing the ischaemic limbs' temperature for up to three hours.

The application of hypothermia immediately prior to the tourniquet application gave significant protection to the muscle. In the hypothermic group this was shown by :

1. A slowing of local muscle metabolism during the ischaemic period
2. Less muscle damage during the ischaemic period itself, based on biochemical results immediately after tourniquet release.
3. Equal muscle and skin temperatures in the ischaemic and control limbs after tourniquet release, indicating a smaller inflammatory response
4. An increased rate of tissue recovery after tourniquet release, based on biochemical results.
5. Enhanced muscle viability ten days after the initial tourniquet application, based on the results of muscle biopsies.

Thus, these studies provide strong evidence that local hypothermia could be a useful clinical modality for the "safe" prolongation of a pneumatic tourniquet application. However, further studies are required to assess its full role in clinical practice.

CHAPTER FIVE

FUTURE DIRECTIONS FOR RESEARCH TO REDUCE TOURNIQUET-INDUCED NEUROMUSCULAR DAMAGE

INTRODUCTION

The studies reported in the previous chapter have shown that hypothermia, at least partially, protects muscle during tourniquet-induced ischaemia. However, it is clear that a number of additional problems exist in the use of the tourniquet and future research should direct attention to these problems.

The five areas that I believe require attention are :

1. Determination of the "safe" tourniquet period
2. Determination of the optimum tourniquet pressure
3. Attention to the possible neurological damage caused by the tourniquet
4. Studies of the effects of tourniquet application on clotting profiles and platelet aggregation
5. Standardization of testing of pneumatic tourniquet apparatuses.

Of these, I have tested a series of pneumatic tourniquet apparatuses and have drawn up a protocol for their testing in clinical practice.

5.1. THE SAFE TOURNIQUET PERIOD

What is a safe tourniquet time?

Most authors agree with Klenerman (1962) that a limb which has had a tourniquet left on, either accidentally or as a "first aid" measure, for more than six hours, will almost certainly have to be amputated. There is, however, much debate in the literature regarding the length of time a tourniquet can be left on "safely".

Santavirta et al. (1978a) analysed 1000 consecutive lower limb operations performed under tourniquet at the University Hospital Helsinki, and found the average length of tourniquet duration to be 74 ± 29 minutes, ranging from 58 ± 16 minutes for menisectomies to 131 ± 11 minutes for total knee replacements.

Seki (1980) used hypothermia prior to tourniquet application, and suggested four hours to be a safe time for upper limb ischaemia. On the basis of his metabolic studies, Klenerman suggested 3 hours to be the maximum safe tourniquet time (Klenerman 1962, 1980, 1982), as did Parkes (1973). In a review of 1500 patients who had tourniquets applied to the upper limb for two hours or less, Flatt (1972) concluded that two hours was a practical and safe duration for upper arm ischaemia. Shaw-Wiglis (1971) found that after a tourniquet time of two hours, blood pH levels took progressively longer than 15 minutes to return to control levels and therefore also concluded that two hours was the upper limit of safety.

Chiu et al. (1976) and Heppenstall et al. (1979), using blood pH and creatine kinase activity as markers of muscle damage in dogs, suggested that the total tourniquet time could be safely increased to three hours, if the occlusion was interrupted by 15 minutes after each hour of ischaemia. Santavirta et al. (1975b) have suggested that striated muscle withstands tourniquet ischaemia of two hours well. In contrast, Rorabeck and co-workers (1980) who studied nerve conduction velocities and recoveries during tourniquet application on dogs, suggested a maximum tourniquet time of only 75 minutes; less for patients with fat limbs

because of the greater shear stress. Heppenstall et al. (1979) agreed with this time limitation. Bruner (1970) suggested one hour to be a safe, but NOT harmless, tourniquet duration for upper limb surgery, whereas Eriksson (1981) even suggests that the tourniquet should be avoided altogether in the sportsman undergoing knee surgery, as do Dobner and Nitz (1982).

Thus, the various 'authorities' have widely differing views on the safe duration of a tourniquet application, ranging from its avoidance altogether, to up to 4 hours. The intermittent release of the tourniquet as recommended by some, is viewed as clinically impractical by the majority of surgeons because of the poor operating field thus created and the difficulty in closing the odematous wound (Flatt 1972).

5.2 THE OPTIMUM TOURNIQUET PRESSURE

It is difficult to measure the pressure exerted by an Esmarch bandage tourniquet. There is no standard size for the bandage itself, although it is usually of the order of 2 m long x 76 mm wide x 1 mm thick. There is also no standard arm or leg to which it is applied, nor a standard surgeon to apply it. Griffiths and Hamilton (1970) found that four turns on a limb of 382 mm circumference exerted an average incremental pressure of 180 mmHg for each turn. However, pressures of up to 1000 mm Hg have been measured when the Esmarch bandage was put on 'enthusiastically' over a small limb.

Even using the calibrated pneumatic cuff tourniquet, there is no scientific approach to the pressures that should be applied with regard to

the size and shape of the limb, the size of the cuff and the patient's systolic blood pressure, etc. Klenerman (1980) stated that "for the cuff pressure to equal blood pressure, the cuff width should exceed the diameter of the limb by 20%." However, the same author, (Klenerman 1982), suggested that in normotensive patients who are not grossly obese or very muscular, a tourniquet pressure of double the systolic pressure is necessary to occlude the circulation and yet allow for pressure fluctuations during the operation. A pressure of 300 mmHg for the upper limbs and 500 mmHg for the lower limbs, as recommended by Campbell (1953), appears to be most commonly used. This is also the pressure presently recommended by the Walter Kidde Company, makers of the widely used Kidde pneumatic tourniquet. Whilst this pressure is known to produce a bloodless field, it has been suggested that a tourniquet pressure 35 - 100 mmHg above the patient's systolic blood pressure would be more logical and safer (Sanders 1973, Klenerman 1980 and Adams 1976). These recommendations have been utilized by McEwen and McGraw (1982) to construct a microprocessor-based tourniquet coupled with a sphygmomanometer cuff measuring the patient's blood pressure. The tourniquet pressure is regulated to remain 50 mmHg above the patient's systolic pressure throughout the operation and thus the total tourniquet pressure used is greatly diminished.

The development of such adaptive equipment is very important and could become standard equipment for all orthopaedic and casualty theatres, if it is shown to improve the safety of the tourniquet procedure. However, the expense of the unit, would probably limit its purchase in the foreseeable future.

Thus it appears that the arbitrarily assigned tourniquet pressures of 500 mmHg for the lower limb and 300 mmHg for the upper limb are widely used at present. However, workers are now investigating whether such high pressures are necessary to create a bloodless field. In the future a more logical approach to setting a tourniquet pressure would take into account the patient's limb size, his or her systolic blood pressure and the properties of the pneumatic cuff itself. This would lessen the total tourniquet pressure applied and may help to decrease the damage caused to the underlying tissue.

MEASUREMENT OF THE TISSUE PRESSURE EXERTED BY THE TOURNIQUET

No-one has yet measured the actual tissue pressures exerted by the tourniquet. It is this pressure which occludes the artery and, as long as the pressure remains above arterial pressure, a bloodless field will result distal to the cuff. It should, theoretically, be possible to measure pressures under the tourniquet cuff and formulate an equation for the ideal cuff pressure for each individual patient. This equation would take into consideration the circumference of the patient's limb, the patient's systolic blood pressure and the pneumatic tourniquet cuff width. The equation would have to allow a safety margin for fluctuations in the patient's blood pressure and hysteresis in the tourniquet apparatus itself.

METHODS OF MEASURING TISSUE PRESSURE

Attempts at monitoring intramuscular tissue pressure have been made since Landerer in 1884 whose needle manometer technique, with various modifications (Burch and Sodeman 1965, McMaster 1941, Matsen et al. 1976), has also been used to diagnose compartmental pressure syndromes (Whitesides et al. 1975, Matsen et al. 1976).

The various techniques of intramuscular pressure measurement and their problems as related to pressure measurements under a tourniquet are :

The Capsule Method

Guyton et al. (1971) surgically implanted a porous capsule in the tissue to be studied. After leaving the area to heal for several weeks, the fluid within the capsule was assumed to have reached equilibrium with the surrounding fluid. A needle, to which was attached a pressure measuring device, was then inserted into the capsule. The pressure so measured was considered to be the interstitial tissue pressure of the area.

This technique is obviously not well suited to tourniquet experiments because of the surgical implantation required, the long equilibration time and the fact that only one area can be monitored. The method has also been criticised because the observed pressure is influenced by the

osmotic gradient between the fluid inside and the fluid outside the capsule, which may alter under external pressure forces (Stromberg and Wiederhielm 1970).

The Balloon Method

In this technique, the tissue pressure is measured by a flaccid-walled balloon surgically implanted in the muscles and attached to a pressure monitor (Johnson et al. 1939). Various authors have also used this method to monitor the pressure, using the subject's veins as the "balloon" (Ryder et al. 1944, Kjellmer 1964).

The Wick Method

Scholander (1968) described a simple wick technique which he used to study pressure change problems in various creatures, including dehydration in toads, tourniquet oedema in crocodiles and the hydrostatic compensatory mechanism of snakes, amongst others.

The wick catheter has also been used experimentally and clinically to measure and monitor intra-tissue pressures (Mubarak et al. 1976, Miller et al. 1979, Ladegaard-Pedersen 1970). The method is relatively simple, and is a modification of an open bore needle technique in which cotton fibrils protrude from the bore of a catheter assembly. This provides an extensive contact area for fluid equilibration and prevents ball-valve obstruction. The advantages are that it is minimally invasive,

provides for continuous monitoring and is cheap to produce. In addition, the wick itself cannot act as an osmometer (Mubarak et al. 1976), because it is completely permeable. To prevent clotting around the wick fibrils and to decrease oedema formation, the threads are dipped in a solution of adrenaline and heparin before insertion.

The disadvantages are that it theoretically measures only fluid tissue pressure, as opposed to total tissue pressure. The response time is slow, 4 - 10 minutes being necessary to equilibrate for pressure increments of 2 - 3 mmHg, and the technique can only be used in non-traumatised tissue.

Infusion Techniques

These methods measure the pressure necessary to infuse fluid or air into the tissue. When there is excessive free fluid in the tissue, the solid elements are separated and fluid tissue pressure and total tissue pressure become equal.

The disadvantages with this method are that the measurements are not continuous. A manometer and an air fluid meniscus must be observed simultaneously to detect the pressure at which fluid first begins to flow into the tissue, and thus there is the possibility of significant

observer error. Satisfactory measurements can also only be made in non-traumatised tissue (Snashall and Boother 1974). Mubarak et al. (1976) maintain that this technique is inaccurate, tending to over-read at low pressure and under-read at high pressures.

Matsen et al. (1976) described a continuous infusion technique using an infusion pump which keeps the needle open with as little as 0,7 cc of fluid per day. The authors claim this to be a safe, accurate and simple method of continous monitoring of intra-tissue pressure for the recognition of compartmental pressure syndromes.

Solid State Pressure Probe

When used to monitor intra-muscular pressure, Mubarak et al. (1976) found solid state pressure probes to be highly dependent on temperature. Pressure recordings of the same muscle compartment often gave quite different results with little consistency in the readings.

CONCLUSIONS

Various methods for measuring tissue pressure are available and all appear to have their problems and limitations. A useful contribution to the debate on safe tourniquet pressures would be the standardization of pressures needed for the variety of subject shapes one encounters in clinical practice. I suggest that the actual pressures exerted by the different types of tourniquet around differently shaped limbs should be measured by whichever of the above techniques is found to be most appropriate. My own feeling is that the Wick method, as described by

Scholander (1968) and modifed by Mubarak et al. (1976), is the best method available.

5.3 ADDITIONAL STUDIES OF PARTIAL SKELETAL MUSCLE DENERVATION AFTER TOURNIQUET PROCEDURES

There are three studies which show that 60-70% of patients have partial denervation in quadriceps muscle after menisectomy under tourniquet (Weingarden et al. 1979, Saunders et al. 1979, Dobner and Nitz 1982). The electromyographic abnormalities that were reported included spontaneous action potentials, sharp 'a' waves, fibrillation potentials and motor unit deficits.

These studies have important implications for the future use of the tourniquet. A sportsman who has been subjected to an operation in which a tourniquet was applied, even for a few minutes, may have had his ability for rapid rehabilitation to full muscular strength seriously prejudiced. Any weakness of the femoris quadriceps, for example, may predispose to a further, and perhaps more severe, injury should the athlete return to sport prematurely. Thus it is important that further trials be carried out to ascertain if the incidence of electromyographic (EMG) abnormalities is as high as that reported six weeks after menisectomy under tourniquet. Femoral nerve conduction studies should also be carried out at the same time.

The quantitative effect that any denervation has on the muscle functioning could be recorded by means of an isokinetic testing machine (Cybex, Lumex Inc., New York, U.S.A.). Follow-up of abnormalities would

include monthly muscle and electromyographic testing until full recovery has occurred.

A study of this nature would be of great importance in ascertaining:

1. the percentage of patients who have unrecognized nerve damage after tourniquet procedures, and
2. the correlation between the nerve damage and objectively-measured muscle function. Both these factors are of utmost importance in deciding whether or not a sportsman should have surgery under tourniquet.

5.4 STUDIES ON THE EFFECTS OF TOURNIQUET APPLICATION ON CLOTTING PROFILES AND PLATELET AGGREGATION

Various authors have proposed that platelet aggregation is affected by tourniquet application (Stebhens and Biscoe 1967, Zahavi et al. 1980, Chen et al. 1982). Patients with ischaemic heart disease were found to have a significant increase in platelet aggregation after tourniquet application, due to a decrease in prostacyclin generation and an increase in thromboxane A_2 liberation (Chen et al. 1982). Healthy subjects, in contrast, showed an increase in prostacyclin generation as well as thromboxane liberation; changes which would tend to oppose platelet aggregation.

This finding may account for differences in the prevalence of deep vein thrombosis reported after tourniquet application. Some authors have reported an increased (Price et al. 1980), whilst others have reported a decreased prevalence of deep venous thrombosis (Klenerman et al. 1977,

Fahmy and Patel 1981, Kroese and Stiris 1976, Simon et al. 1982), when operations performed under tourniquet were compared with those performed without tourniquets.

Clearly, additional studies are required to answer these questions. One approach would be to study patients who are scheduled to undergo surgery on the lower limb in which a tourniquet is to be used. A full medical history would be taken prior to the operation with an emphasis on signs and symptoms of ischaemic or peripheral vascular disease. Blood samples for platelet aggregation and clotting studies would be taken prior to tourniquet release 5, 30 minutes and 60 minutes after tourniquet release. The study could be extended to investigate the correlation between clotting parameters and the incidence of deep vein thrombosis as detected by Doppler, fibrinogen or venogram studies.

This study would show whether changes in the blood clotting profiles are dependent on the pre-operative status of the patient. If found to be so, surgeons would have to review seriously the advisability of the use of the tourniquet in certain patients. If necessary, such patients might have to be pre-treated with an anti-platelet aggregation drug, such as low dose aspirin.

5.5 THE STANDARDISATION OF TESTING PNEUMATIC TOURNIQUET APPARATUSES

Introduction

Several authors (Bruner 1951, Hamilton and Sokoll 1967, Prevoznik 1970, Fry 1972, Calderwood and Dickie 1972) have reported nerve damage caused by faulty tourniquet gauges. On testing, some of these gauges

under-read by as much as 500 mmHg. Fry (1972) conducted random checks on tourniquet equipment in every-day use and found 20 of 31 to be defective.

Certain manufacturers (Walter Kidde & Co. Inc.) recommend that their apparatus should be tested monthly against a mercury manometer. These tests consist of recording the accuracy of the tourniquet gauge reading at pressures of 100 and 300 mmHg and the ability of the apparatus to hold a constant pressure of 300 mmHg for 20 minutes. Hurst et al. (1981) conducted such tests on machines in routine use and found two out of seven to be defective. The pressure applied by one machine increased by 500 mmHg after only ten minutes. A more stringent testing procedure, in use in Vancouver Hospital, Canada, was outlined by McEwen (1981).

I, therefore, decided to draw up a protocol which included most of the described tests and to study the tourniquet apparatuses in clinical use in six hospitals in the Western Cape.

Materials and Methods

The test gauge was a digital readout pressure transducer (see Equipment Chapter 4.2A) especially constructed for the experiments. It was re-calibrated regularly against a mercury manometer.

A copy of the testing protocol and the pre-marked form, together with a watch and pen, were taken to the surgical theatres where the Kidde (reg) apparatus was in regular use. The Kidde tourniquet apparatus (Model 400) consists of a gauge which can be pre-set to deliver the required

pressure to an inflatable cuff. The pressure is produced by the vaporisation of a volatile liquid (freon) contained in the reservoir of the apparatus. This reservoir is supplied by freon contained in a renewable container connected at the rear. The Kidde pneumatic tourniquet apparatus was chosen for the study as it is the most popular of the automatic apparatuses in clinical use in the Western Cape.

The testing protocol was as follows :

The Kidde tourniquet apparatus was connected to the test pressure gauge by a three-way tap. The accuracy of the apparatus gauge was checked by comparing it to the pressure recorded on the test gauge, when the apparatus gauge was set at pressures of 100, 200, 300, 400, 500, 600 and 700 mmHg. The effect, if any, of tapping on the tourniquet gauge was noted.

A pressure of 500 mmHg was then set on the tourniquet gauge, the test gauge pressure noted and the three-way tap turned to place the test gauge out of circuit. After 10 minutes, the three-way tap was opened to the test gauge and the pressure reading again recorded. The difference between the initial and second readings was taken to be a measure of the ability of the apparatus to maintain a pre-set pressure (i.e. its stability).

In the next test a rubber bulb from a sphygmomanometer was placed in parallel to the test gauge and tourniquet apparatus. A pressure of 300 mmHg was set on the tourniquet gauge and the true pressure recorded from the test gauge. Using the bulb, the pressure in the apparatus was

gently increased, thus imitating a slow continued pressurization of the pneumatic cuff due to a defective valve. A plateau pressure was reached, indicating blow-off of the safety valve and this pressure was recorded from the test gauge (Reading 1). The pressure in the system was then released via the bulb, imitating a leak in the cuff, until a second plateau pressure was reached which indicated the pressure stabilising mechanism had been activated (Reading 2). The difference between the two readings was taken as an indication of the state of the release valve mechanism, the so-called hysteresis of McEwan (1981). The test was then repeated, commencing at a tourniquet gauge reading of 500 mmHg.

The final test was a thorough visual inspection of the apparatus to check that the filling reservoir was not overfilled and that the pressure tubing, connectors, gauge and cuffs were in good condition.

Results of a survey of hospital tourniquet apparatuses

Six hospitals were visited and a total of thirteen Kidde Tourniquet apparatuses checked (Table 5.1). The following were found:

Accuracy - Acceptable accuracy was taken as $\pm$ 5% as recommended by the Kidde manufacturers. The gauges of eight machines (62%) tended to consistently under-read over the range of pressures tested (Figure 20); one machine under-reading by 350 mmHg.

The effect of tapping the gauge - Acceptable effect $\pm$ 15 mmHg. All the machines passed this test.

Stability - Acceptable stability ± 10% after 10 minutes. All but one machine maintained the set pressure.

Release valve mechanism (hysteresis) - The acceptable difference between readings at both 300 mmHg and 500 mmHg was taken as 250 mmHg (McEwan 1981). Eight machines (62%) showed unacceptable hysteresis.

Visual - One machine had the wrong connectors fitted and two machines had reservoirs which were overfilled. One machine had had a release valve placed in line between the tourniquet apparatus and the cuff. This effectively meant that the pressure gauge was out of circuit and thus not monitoring the actual cuff pressure.

TABLE 5.1 RESULTS OF TESTING OF TOURNIQUET APPARATUSES (n=13)

TEST	ACCEPTABLE ACCURACY	NUMBER FAILED	PERCENTAGE FAILED
Accuracy	± 5%	8	62
Tap	± 15 mmHg	0	0
Stability	± 10%	1	8
Release Valve Mechanism	250 mmHg	8	62
Visual		3	23

Discussion and Recommendations

The manufacturer of the Kidde pneumatic tourniquet apparatus recommends regular monthly checks. Various authors also recommend the checking of the pneumatic tourniquet accuracy against mercury manometer before each operation (Hamilton and Sokoll 1967, Bruner 1970, Flatt 1972). It would seem, however, that these recommendations are not observed, at least in hospitals in the Western Cape, as only two out of 13 apparatuses tested

were found to be satisfactory for all the criteria. This agrees with other random surveys (Fry 1972, Prevoznik 1970, Rorabeck 1980).

Some of the faults found in this survey could be easily remedied as the inaccuracy of the tourniquet gauges tended to be linear at all pressures (Figure 20). Thus, re-zeroing of the needle would restore complete accuracy. However, other faults rendered some machines dangerous, as in the case where a separate pressure release valve had been placed between with the cuff and the tourniquet gauge or where the release valve mechanism was faulty, as found in 8 (62%) of the apparatuses tested.

This study, therefore, showed that there is a need for a series of regular checks to be performed on the pneumatic tourniquet apparatus. I suggest the inclusion of the testing protocol into a surgical theatre's checklist, would be another way to lessen the risk of the tourniquet procedure by removing the "hidden" risk of faulty equipment.

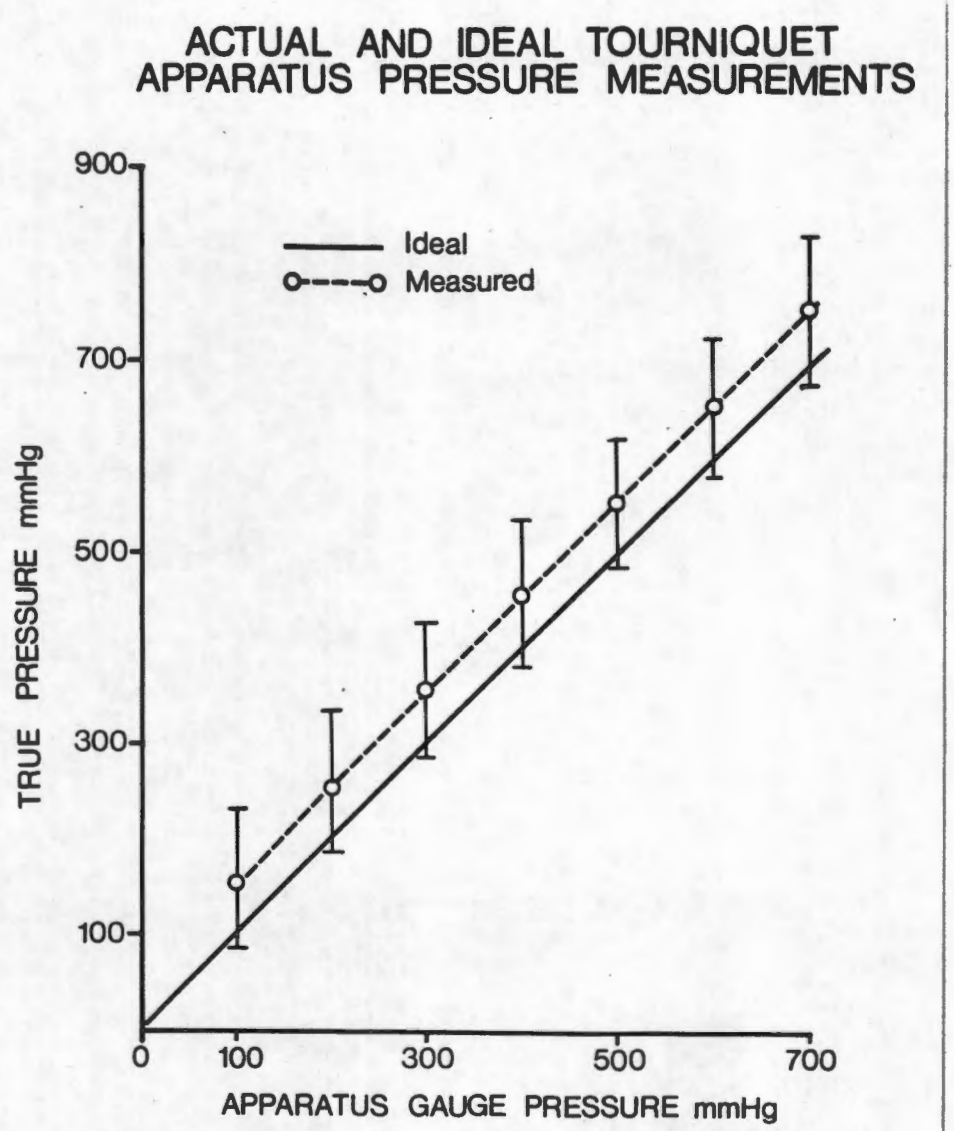


FIGURE 20

Note the true pressures measured on the test gauge are linearly higher at all measured pressures.
Results expressed as mean for thirteen pneumatic apparatuses, plus or minus standard deviation.

CHAPTER SIX

OVERALL SUMMARY AND CONCLUSIONS

1. The protective role of hypothermia during tourniquet-induced muscle ischaemia

This study has established that cold polyglycol gel packs are easy and safe to apply to the tourniquet limb; they produce very adequate local hypothermia which provides partial protection to the ischaemic limb muscles.

However, a weakness of this study was that it was based on the measurement of metabolic and biochemical parameters. An improvement would have been to study morphological differences between the hypothermic and normothermic ischaemic limbs, using the electron microscope. It would have been of interest to combine such a study with histological evaluation of the effect of local hypothermia on the nerve damage caused by the application of a tourniquet. It may then have been possible to correlate observed changes with an electromyographic study of the muscle innervated by that nerve.

A study such as that mentioned above would be important in further clarifying the protective role of local hypothermia during tourniquet application.

2. Further Clinical Studies

Clinical studies are indicated to evaluate various aspects of the pneumatic tourniquet application, namely :

A. The clinical role of hypothermia, produced by the application of cold gel packs, in decreasing neuromuscular damage and extending the "safe" tourniquet time.

B. The clotting and platelet aggregation changes which occur with the use of the pneumatic tourniquet. The effect of local hypothermia on these parameters could also be studied

C. The feasibility of creating an equation to enable the surgeon to individualize the tourniquet pressure for each patient. Thus, the total tourniquet pressure used during the operation could be safely decreased.

D. The incidence of electromyographic abnormalities in the muscles of patients after operations involving the use of the tourniquet. This could be objectively correlated to muscle weakness and the time taken to full recovery.

Thus, whilst much work has been carried out on the effects of the pneumatic tourniquet, much still requires to be investigated. It is hoped that further clinical studies along the lines indicated will shed more light and make what has become a routine surgical procedure safer for the patient.

APPENDIX I

ANALYTICAL METHODS

APPENDIX 1

BLOOD ASSAYS

I. Sodium and Potassium Levels

4.5 ml of venous blood was collected in a heparinised Vacucontainer (Beston - Dickinson) and agitated gently for a few seconds. The sample was then placed in the fridge (4°C). Within two hours of collection the tube was centrifuged at 2000 R.P.M. for 15 minutes, and the serum pipetted off and stored in the fridge.

The sodium and potassium levels in the serum were measured using a flame photometer (Instrumentation Laboratory Flame Photometer 543), with lithium as the standard reference..

II. Calcium Levels

1½ ml of blood was placed in an Eppendorff tube and allowed to clot. The tube was then centrifuged at 2000 R.P.M. for 15 minutes. The supernatant serum was pipetted off and placed in a fresh Eppendorff tube, stoppered and placed in the freezer (-20°C) until analysis. The total calcium was measured using an Atomic Absorption Spectrophotometer (Varian model AA 1275) at an absorption of 422.7n.m., with a plasma standard (Versatol General Diagnostics) diluted 1 in 30 in Harthaium (B.D.H.) (La100g/ml).

III. Hydrogen Ion Concentration (pH)

2 ml of blood was drawn into a heparinised syringe. A needle was attached and bent over to prevent equilibration of the blood with room air. The sample was then analysed within five minutes using a pH meter (Radiometer M73, Copenhagen) coupled with a BM5 Mk2 Micro System. The apparatus was standardised using pre-made solutions of pH7,383 and pH 6,841.

IV. Lactate Levels

1.2 ml of blood was placed in a previously weighed plastic test tube containing 2 ml of 0,6N perchloric acid (PCA). The tube was agitated to mix thoroughly, weighed and placed in the fridge. Within two hours the lactate was spun at 2000 RPM for 15 minutes and the supernatant decanted off and stored in the fridge (4°C) until the assays were performed.

Assay Method

Cuvettes were made up using 3 blanks and 2 standards as follows :

	Std	Blank	Test
Hydralazine buffer	1,0 ml	1,0 ml	1,0 ml
NAD	0,1 ml	0,1 ml	0,1 ml
PCA	-	0,1 ml	-
LDH	0,01 ml	0,01 ml	0,01 ml
Supernatant	-	-	0,1 ml
Standard (Std)	0,1 ml	-	-

The solutions were mixed (vortex mixer Fissons BP 931263) and allowed to equibrate to room temperature for 30 minutes.

The absorption at 340 nm was then read using a spectrophotometer (Beckman Instruments, Spectrophotometer Model 35), zeroed against distilled water.

The following calculation was then used :

$$\frac{\text{Total volume in cuvette}}{\text{Volume of supernatant}} \times \frac{\text{vol. of P.C.A. + blood}}{\text{vol blood}} \times \frac{1}{6,22}$$

6,22 = molar extinction coefficient of NADH)

to give the concentration of lactate in /mole/ml

V. Creatine Kinase (CK) Activity

6 ml of blood was collected in a tube with an inert barrier and clot activating medium at the base (vacucontainer SST6510), left to clot at room temperature for half an hour, and then placed in the fridge. The blood was centrifuged at 2000 rpm for 15 minutes, the serum decanted off and stored in the fridge until assayed within five days. Porcine CK activity is reported to be stable in stored serum until well after five days (Mitchell et al 1975). 15 µl of the sample was then diluted with 50 µl of distilled water, 350 µl of reagent (NAC activated Monotest, Boehringer Mannheim cat No. 181188) was added and the absorption at 340 nm read on a spectrophotometer (Centachem System 400).

MUSCLE ASSAYS

I. Glycogen Content

The weighed muscle sample was macerated with 1 ml KOH (40%) and added to a plastic tube. The tube was placed in a water bath at 100°C for 30 minutes, after which 4 ml of 95% ethanol was added to the solution and the tube was again placed into the water bath for 30 minutes to precipitate the glycogen. The solution was left overnight in the fridge (4°C) and then the supernatant removed after centrifuging (10 minutes at 5000 r.p.m.). One ml 2N HCl was added to the precipitate to hydrolyse the glycogen to glucose and the solution was placed in the water bath at 100°C for 3 hours. 0,2M Tris buffer was added to the solution to bring the pH to 7,5, 200 µl of the resultant was mixed with 2,8 ml of the reagent mix (see below) and the absorption read at 340 nm (Beckman Spectrophotometer Model 35). The above procedure was carried out over three successive days.

REAGENT MIXTURE

Reagent Mixture	Per Cuvette
Tris buffer 0,2M pH 7,5	1ml
ATP 20 mM	0,1 ml
$MgCl_2 6H_2O$ 1M	0,1 ml
NADP 1% (TPN)	0,1 ml
Distilled Water	1,5 ml
	2,8 ml

200 µl of reagent mix was also added to 200 µl of 1mM glucose standard and 200 µl of distilled water (used as the blank) and their absorptions at 340 nm recorded.

10 µl of HK/G6PDH suspension (Boehringer Cat. No. 127825) was added to each cuvette and after standing for 30 minutes the absorption at 340 nm again read.

The glycogen content was calculated from the following formula.

$$\left(\left(\frac{\text{Optical Density difference}}{0{,}414} - \right) - \text{baseline}\right) \times \frac{3(\text{Vol in cuvette})}{\text{wet wt mg}}$$

This gives the glycogen content in mmole glucose equivalents/kg wet weight.

The recovery was calculated by $\frac{\text{Std reading}}{0{,}414} \times 100$

The recovery during the experiments was greater than 92%.

II. Phosphofructokinase (PFK) Activity

The muscle sample was weighed and diluted 1 in 10 with a homogenating buffer consisting of

50 mM triethanolamine HCl

2 mM $MgCl_2$

1 mM EDTA

30 mM Mercaptoethanol

2 mM glycerol : for stabilising

1 mM 2-oxoglyturate : effect

Keeping the tube surrounded by ice, the muscle was then homogenated for 10 secs. (Ultra TURRAX-TP18/10 Janke and Kunkel - Germany, setting 4) and sonicated (Sonifier Model B-12, Branson Sonic Power Company) for 15 seconds. It was then centrifuged for 1 minute at 4°C (2000 r.p.m.) and the supernatant fluid decanted off for measuring.

Next 10 1 of the supernatant fluid was added to a cuvette with the reagent mixture which consisted of :

1 ml Tris - HCl - KCl - $MgCl_2$ - BSA buffer pH 8.2

10 1 ATP 100 mM

10 1 AMP 200 mM

10 1 NADH 100 mM

10 1 F-6-P 100 mM

* 5 1 aldolase

* 5 1 x glycerin - 3 - phosphate dehydrogenase

* 5 1 1:10 Trisephosphate isomerase

* added just prior to the addition of the supernatant fluid

The mixture was agitated and read to extinction at 340 mm, (Beckman spectrophotometer - Model 35). The milli Absorbance Units per minute was calculated from the slope of the curve.

The PFK activity was calculated according to the equation

$$\frac{\text{m.A.U.}}{6,2} \times \frac{\text{total vol cuvette (ml)}}{1000} \times \frac{1000}{\text{Vol extract used (ml)}} \times \frac{1}{\text{tissue wt (mg)}} \times \text{Vol Homogenising medium (ml)}$$

m.A.U. - milli absorbance units in one minute at 340 n.m.
This gave the value of PFK activity in mol/min/g wet wt.

Storage of reagents

ATP, AMP, NADH, and F-6-P were kept in the freezer (-20°C) and the remaining reagents were kept in the fridge (4°C).

APPENDIX 2

STATISTICS

APPENDIX 2

STATISTICS

The data were analyzed by an analysis of variance. Homogeneity of variance was tested using Bartlett's criteria, where the variances lacked homogeneity at p 0,05 the raw data was transformed (either squared root or log). Acceptance intervals of the mean (allowance) was calculated using :

$$AP = tp\sqrt{Ms \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}$$

A = Acceptance interval

p = Probability value

t = Student's t value

MS = Mean square within the cell

n_1 = Sample size of one mean

n_2 = Sample size of second mean

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